Clinical Pharmacy Slides; Organized & Simplified
by **Haris Saeed**

# CLINICAL PHARMACY-II

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|---|---|
| Student Name | |
| Class: | 5th Professional Year |
| Section: | |
| Roll No. | |
| Mobile No. | |

# Index

**PHARMACEUTICAL CHEMISTRY-IV (MEDICINAL CHEMISTRY) (Practical)**

**Paper 6** **Marks 100**

**NOTE:** Practical of the subject shall be designed from time to time on the basis of the above mentioned theoretical topics and availability of the facilities e.g. Estimation of functional groups; Carboxylic, Hydroxy, Amino and Nitro groups; Determination of Molecular weights of Organic Compounds. Synthesis of Paracetamol, Salicylic Acid, Methyl salicylate, Azobenzene, Benzoic Acid, 5-Hydroxy-1, 3-benzoxazol-2-one, Aspirin, P-nitrosophenol, 3-nitrophthalic acid, Chloro-benzoic acid. Assay of the Drugs like Sulpha drugs, Aspirin, Paracetamol, Benzyl Penicillin. Inorganic Preparations **(Note:** A minimum of 20 practicals will be conducted).

**PHARMACY PRACTICE-VI (CLINICAL PHARMACY-II) (Theory)**

**Paper 2** **Marks 100**

1. **RATIONAL USE OF DRUGS:** Rational Prescribing, Rational Dispensing, Problems of Irrational Drug Use, Learning about drug use problem, Sampling to study drug use, Indicators of drug use.

2. **INTRODUCTION TO ESSENTIAL DRUGS:** Criteria for selection, Usage and Advantages. Development of EDL.

3. **DRUG UTILZATION EVALUATION & DRUG UTILIZATIONREVIEW (DUE/DUR):** Development of protocol of use of few very low therapeutic index drug groups like Steroids, Vancomycin and Cimetidine.

4. **CLINICAL PHARMACOKINETICS:** Therapeutic Drug Monitoring of Digoxin, Theophyline, Gentamycin, Lithium, Phenytoin, Cabamazepine, Phenobarbitone, Valproic Acid, Cyclosporins and Vancomycin.

5. **PHARMACEUTICAL CARE, ITS SCOPE, MANAGEMENT AND APPLICATION OF CARE PLAN:**

6. **CLINICAL THERAPEUTICS:** General Strategy: Terminology of Disease. Management and Treatment. Drug Selection.

7. **CLINICAL TOXICOLOGY:**

   (a) General information. Role of pharmacist in treatment of poisoning and general management of poisoning & over dosage. Role and Status of Poison Control Centre.
   (b) Antidotes and their mechanism of action.

8. **SAFE INTRAVENOUS THERAPY & HAZARDS OF IV THERAPY**

9. **NON-COMPLIANCE:** Definition, introduction and importance, Extent of non-compliance, Methods of assessment, Reasons for non-compliance, Strategies for improving compliance.

**10. DISEASE MANAGEMENT:**

- Unit V: Central nervous system unit (Stroke, Epilepsy, Psychosis)
- Unit VI: Infectious diseases (Meningitis, tuberculosis, dermatological infections, Rabies, Urinary track infection, Malaria fever, Typhoid fever, Fungal infections of skin, AIDS, Dengue fever, Common Cold, Pharyngitis & Tonsillitis, Conjunctivitis)
- Unit VII: Endocrinology Unit (Diabetes Mellitus, Hyper/Hypo-thyroidism, pituitary gland non-malignant disorders)
- Unit VIII: Oncology Unit (Types of tumors, Brief introduction to oncological diseases e.g. prostate cancer, breast cancer, lungs cancer )
- Unit IX: Nephrology Unit (Renal failure, nephrotic syndrom)
- Unit X: Hematology Unit (Bleeding disorders/coagulopathies/clotting disorders e.g. thrombocytopenia, hemophilia, Vit. K deficiency, Anemia).

**PHARMACY PRACTICE-VI (CLINICAL PHARMACY-II) (Practical)**

**Paper 7** **Marks 100**

- Clerkship in the Clinical Setting. A project Related to Clinical Pharmacy Practices will be completed by the students and will be evaluated by the external examiner.

- Student are required to take/present verbal presentation, communication, written and problem-solving skills, critical analysis of data and provision of care through a weekly conference and projects

**PHARMACEUTICS-VII (PHARMACEUTICAL TECHNOLOGY) (Theory)**

**Paper 3** **Marks 100**

1. **PRINCIPLES OF PHARMACEUTICAL FORMULATION AND DOSAGE FORM DESIGN:**
   Need for dosage form; Pre-formulation Studies; Product Formulation.

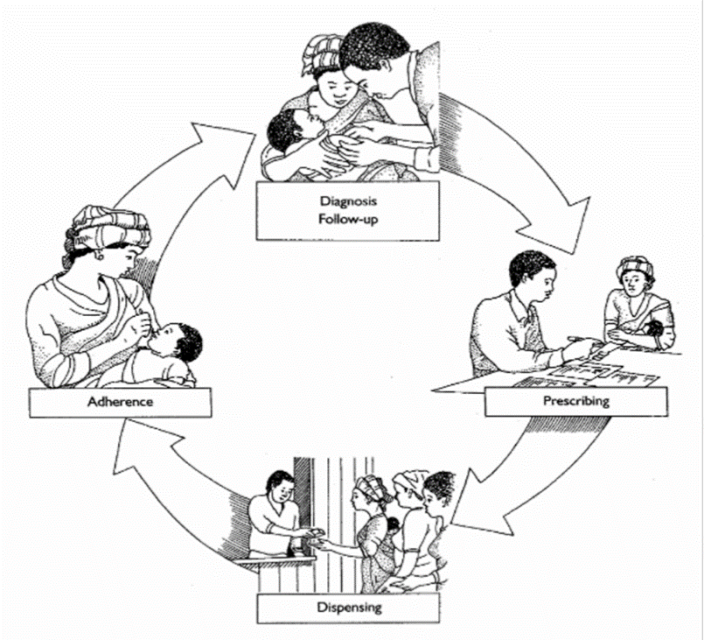
2. **ADVANCED GRANULATION TECHNOLOGY (DESIGN & PRACTICE):**
   Spray Drying Granulation Technology; Roller Compaction Technology; Extrusion/Spheronization as a Granulation Technique; Single-Pot Processing **Granulation Technology:** Rapid Release Granulation Technique; Particle Coating by Centrifugation Granulation Technology.

3. **POLYMERS USED IN DRUG DELIVERY SYSTEMS:**

4. **NOVEL DRUG DELIVERY SYSTEM (DDS):**
   Sustained/ Controlled Release Drug Delivery System
   i. Microencapsulation technique
      - Coacervation
      - Solvent evaporation
      - Interfacial polymerization
      - Spray drying
   ii. Developmental aspects of Matrix and Reservoir Systems

# Rational Use of Drugs (RDU)

## Drug Use Process & Importance of RDU




### Factors Leading to the Realization of RDU

✓ **Drug explosion** – Increased availability of drugs
✓ **Efforts to prevent resistance** – To avoid antimicrobial resistance
✓ **Growing awareness** – Among healthcare providers and patients
✓ **Increased cost of treatment** – Need for cost-effective therapy
✓ **Consumer Protection Act** – Legal measures to ensure safe drug use

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## Irrational Use of Drugs

| Type of Irrational Use | Description |
|---|---|
| **Under-prescribing** | Prescribing less than the required dose or duration |
| **Incorrect prescribing** | Wrong drug, dose, route, or frequency |
| **Extravagant prescribing** | Prescribing unnecessary or expensive drugs |
| **Over-prescribing** | Using more medication than necessary |
| **Multiple prescribing** | Prescribing multiple drugs without proper justification |
| **Unproven efficacy** | Using drugs with questionable effectiveness |

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## Definition of Rational Drug Use

✓ Right **Drug**
✓ Right **Patient**
✓ Right **Time**
✓ Right **Dose**
✓ Right **Route**
✓ **Economical** choice

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## Steps to Achieve RDU

| Step | Action |
|---|---|
| **Step I: Identify Patient Problem** | Take a detailed history, assess complaints, review drug history |
| **Step II: Diagnosis** | Essential prerequisite for rational prescribing |
| **Step III: Set Therapeutic Objective** | Define the treatment goal |
| **Step IV: Select Treatment** | Consider lifestyle changes and drug selection based on **safety, efficacy, cost, and ease of administration** |
| **Step V: Start Treatment** | Implement prescribed therapy |
| **Step VI: Monitor Treatment** | Assess the treatment response |
| **Step VII: Conclude Therapy** | Stop or modify treatment as needed |

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## Components of an RDU Program

| Component | Details |
|---|---|
| **1. Teaching of Basics** | Pharmacology, Therapeutics, Guidelines, Problem-based learning |
| **2. Essential Drug Concept** | Essential Medicine List (EML), Drug selection, Formulary |
| **3. Drug Information** | Educating physicians, public awareness (newsletters, media), resisting marketing pressure |
| **4. Drug Use Study** | Monitoring prescribing patterns, assessing influencing factors |

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## Factors Influencing Medicine Use

| Category | Factors |
|---|---|
| **Patient & Community** | Awareness, adherence, affordability |
| **Prescriber & Dispenser** | Training, work environment, prescribing habits |
| **Policy & Regulations** | National drug policies, legal framework |
| **Drug Supply System** | Availability, affordability, and distribution |

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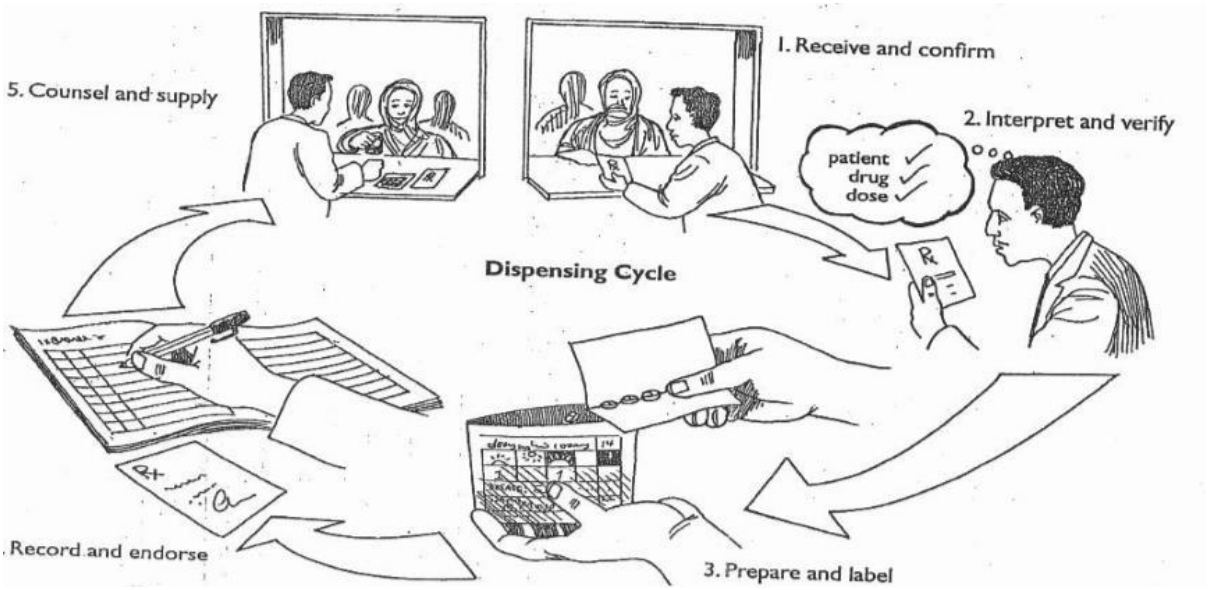
## Rational Prescribing Steps

| Step | Description |
|---|---|
| **1. Specific Diagnosis** | Identify the exact medical condition |
| **2. Consider Pathophysiology** | Understand the disease mechanism |
| **3. Therapeutic Objective** | Define what the treatment aims to achieve |
| **4. Drug of Choice Selection** | Choose the most effective and safe drug |
| **5. Dosing Regimen** | Determine the correct dose, frequency, and duration |
| **6. Drug Action Monitoring** | Observe effects and adjust as needed |
| **7. Patient Education** | Inform about drug use, side effects, and adherence |

## Dispensing Cycle:




## Dispensing Process

| Step | Description |
|---|---|
| **1. Receiving of Prescription** | Accepting the prescription from the patient or caregiver |
| **2. Interpretation of Prescription** | Understanding the prescribed medications and instructions |
| **3. Checking of Prescription** | Ensuring correctness, legality, and appropriateness of the prescription |
| **4. Filling of Prescription** | Selecting and preparing the required medication |
| **5. Labeling of Prescription** | Providing essential details like drug name, dosage, and instructions |
| **6. Handling of Prescription** | Dispensing the medication to the patient with counseling |
| **7. Records** | Maintaining a record of dispensed medications |
| **Final Step** | **Poor or uncontrolled dispensing can be hazardous** |

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## Irrational Use of Drugs

| Cause | Factors |
|---|---|
| **1. Drug Selection** | Inappropriate choice of medication |
| **2. Patient Characteristics** | Age, gender, comorbidities, and compliance |
| **3. Lack of Information** | Inadequate knowledge of the drug or condition |
| **4. Incorrect Prescribing** | Wrong drug, dose, or frequency |
| **5. Expensive Drugs** | Overprescribing costly medications without necessity |

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## Factors Responsible for Irrational Use

✓ **Patients** – Self-medication, demand for unnecessary drugs
✓ **Prescribers** – Lack of knowledge, incentives from pharma companies
✓ **Workplace** – Unregulated practices, lack of monitoring
✓ **Drug Regulations** – Weak policies, ineffective implementation

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## Problems of Irrational Use

✓ **Quality of Life (QOL)?** – Poor outcomes due to incorrect drug use
✓ **Wastage** – Financial and resource loss
✓ **Adverse Drug Reactions (ADRs)** – Increased side effects and complications
✓ **Cost** – Increased treatment expenses

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## Solutions to Irrational Use

| Solution | Approach |
|---|---|
| **Best Practices** | Following evidence-based medicine |
| **Guidelines & Standards** | Adhering to international treatment protocols |
| **Drug Regulations** | Strengthening policies and monitoring drug use |

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## Drug Use Indicators

✓ **Definition** – Objective measures to assess drug use in a country
✓ **Purpose** – **Planning, Supervising** drug use practices
✓ **Origin** – Introduced at **1985 WHO Nairobi Conference**

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## Objectives of Drug Use Indicators

✓ Describing **drug use patterns**
✓ Assessing **prescribing behavior**
✓ Evaluating **intervention impacts**

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## Types of Drug Use Indicators

| Type | Focus |
|---|---|
| **Prescribing Indicators** | Drug prescriptions, dosage, adherence to guidelines |
| **Patient Indicators** | Patient adherence, medication safety |
| **Facility Indicators** | Availability of essential drugs, proper storage |

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## Prescribing Indicators

| Indicator | Standard Values |
|---|---|
| **Average number of drugs per encounter** | 1.6 - 1.8 |
| **Percentage of encounters with an antibiotic prescribed** | 20.0 - 26.8% |
| **Percentage of encounters with an injection prescribed** | 13.4 - 24.1% |
| **Percentage of drugs prescribed by generic name** | 100% |
| **Percentage of drugs prescribed from the Essential Medicine List (EML)** | 100% |

Here is the tabulated version of the data:

| Primary Healthcare Centers | Average number of medicines prescribed per patient encounter | Percent medicines prescribed by generic name | Percent encounters with an antibiotic prescribed | Percent encounters with an injection prescribed | Percent medicines prescribed from essential medicines list |
|---|---|---|---|---|---|
| **1** | 3.4 (1.4) | 81.2 | 64.0 | 38.0 | 98.5 |
| **2** | 3.6 (1.5) | 85.1 | 63.0 | 32.0 | 87.6 |
| **3** | 3.4 (1.3) | 83.0 | 87.0 | 21.0 | 89.2 |
| **4** | 3.2 (3.1) | 43.7 | 40.0 | 18.0 | 90.7 |
| **5** | 3.2 (1.4) | 88.5 | 56.0 | 30.0 | 100 |
| **6** | 1.9 (1.0) | 70.0 | 30.0 | 9.0 | 100 |
| **7** | 5.0 (2.3) | 90.0 | 30.0 | 90.0 | 80.5 |
| **8** | 4.3 (2.4) | 76.0 | 28.0 | 28.0 | 100 |
| **9** | 2.9 (0.7) | 66.7 | 29.0 | 43.0 | 100 |
| **10** | 3.4 (1.1) | 82.0 | 61.0 | 27.0 | 87.9 |
| **Mean (SD)** | 3.4 (0.8) | 71.6 (15.7) | 48.9 (20.2) | 27.1 (9.8) | 93.4 (7.1) |
| **ANOVA** | p < .0005 | p < .0005 | p < .0005 | p < .0005 | p < .0005 |

**Notes:**

- *Primary Healthcare Centers:*
  1 = Agha pur, 2 = Jamal channar, 3 = Mubarak pur, 4 = Jhangi wali, 5 = Mithra, 6 = Chak kotoora, 7 = Kud wala, 8 = Khanqah sharif, 9 = Khanu wali, 10 = Kulab

## Patient-Care Indicators

| Indication | Standard Value |
|---|---|
| **Average consultation time (minutes)** | ≥10 |
| **Average dispensing time (seconds)** | ≥90 |
| **Percent of medicines actually dispensed** | 100% |
| **Percent of medicines adequately labeled** | 100% |
| **Percent of patients with knowledge of correct doses** | 100% |

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## Facility-Specific Indicators

| Indication | Standard Value |
|---|---|
| **Availability of essential medicines list or formulary to practitioners** | 100% |
| **Percent of key medicines available** | 100% |

| Primary Healthcare Centers | Average consultation time (minutes) | Average dispensing time (seconds) | Percent medicines actually dispensed | Percent medicines adequately labeled | Percent patients with knowledge of correct doses | Availability of essential medicines list to practitioners | Percent key medicines available |
|---|---|---|---|---|---|---|---|
| **1** | 2.3 (1.5) | 43.1 (34.7) | 87.3 | 100.0 | 67.0 | 100.0 | 90.0 |
| **2** | 2.5 (1.2) | 43.0 (17.1) | 91.1 | 100.0 | 77.0 | 100.0 | 70.0 |
| **3** | 2.4 (1.0) | 36.7 (10.8) | 91.2 | 100.0 | 77.0 | 100.0 | 80.0 |
| **4** | 1.5 (7.7) | 37.9 (20.3) | 30.0 | 100.0 | 30.0 | 100.0 | 90.0 |
| **5** | 2.1 (0.9) | 42.6 (16) | 100.0 | 100.0 | 67.0 | 100.0 | 80.0 |
| **6** | 1.3 (0.6) | 31.3 (14) | 68.3 | 100.0 | 33.0 | 100.0 | 70.0 |
| **7** | 2.9 (1.4) | 30.9 (10.5) | 100.0 | 100.0 | 53.0 | 100.0 | 70.0 |
| **8** | 2.1 (1.2) | 36.9 (25.8) | 91.5 | 100.0 | 64.0 | 100.0 | 90.0 |
| **9** | 3.6 (1.1) | 63.3 (50.7) | 100.0 | 100.0 | 90.0 | 100.0 | 90.0 |
| **10** | 2.0 (0.7) | 37.1 (20.6) | 93.0 | 100.0 | 63.0 | 100.0 | 80.0 |
| **Mean (SD)** | 2.2 (0.8) | 38.0 (12.1) | 90.9 (9.5) | 100.0 | 62.1 (19) | 100.0 | 82.0 (7.9) |
| **ANOVA** | $p < .0005$ | $p < .0005$ | $p < .0005$ | ——[a] | $p < .0005$ | ——[a] | $p < .0005$ |

[a]ANOVA was not applied for these indicators as there was no variation in their values.

Let me know if you need further modifications!

### Research Characteristics

- Research is creative and systematic work undertaken to increase knowledge, including knowledge of humans, culture, and society, and to develop new applications.
- **Key Attributes:**
  - Neutrality
  - Reliability
  - Validity
  - Generalization

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### Research Design

| Category | Types |
|---|---|
| **Observational** | Exploratory, Descriptive, Cohort, Case-Control, Cross-Sectional |
| **Experimental** | Randomized Control Trials |
| **Other Designs** | Qualitative Research, Systematic Reviews |

## Sampling in Drug Use Studies

#### Key Terms

- **Population**: The entire group being studied.
- **Sample**: A subset of the population selected for study.
- **Participants**: Individuals included in the sample.

### Sampling Process

- The process of selecting a sample from a population is called **sampling**.
- **Sampling Errors**:
  - **Systematic Errors**: Consistent errors in the sampling process.
  - **Sampling Bias**: When certain groups are over or underrepresented.

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## Types of Sampling

| Category | Definition |
|---|---|
| **Probability Sampling** | Every unit has an equal chance of selection. |
| **Non-Probability Sampling** | Some units have a higher chance of being selected. |

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## Probability Sampling

| Method | Description |
|---|---|
| **Random Sampling** | Equal chance for all; lottery or computer-generated selection. |
| **Systematic Random Sampling** | Selection at regular intervals from a homogenous population. |
| **Stratified Random Sampling** | Population divided into subgroups (strata), and samples taken randomly. |
| **Cluster Sampling** | Selection from clusters in a wide geographical area. |
| **Multistage Sampling** | Combination of two or more probability techniques (e.g., Cluster + Stratified). |

### Advantages of Probability Sampling

- Reduces systematic errors.
- Minimizes sampling bias.
- Ensures better representation.
- Produces generalizable results.

### Disadvantages of Probability Sampling

- Requires significant effort and time.
- Expensive to conduct.

### Random Sampling

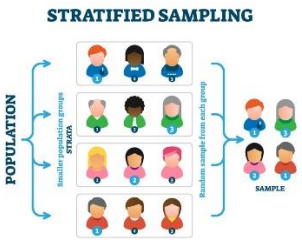
- Every individual has an equal chance of selection.
- Works best with a well-defined, homogenous population.
- Selection methods include lottery systems or computer-generated tables.
- Once selected, participants are approached and interviewed.


### Systematic Random Sampling

- Used for a homogenous population.
- Elements are selected at regular intervals based on time, space, or order.
- Ensures consistency and uniformity in selection.
- Once chosen, participants are approached and investigated.

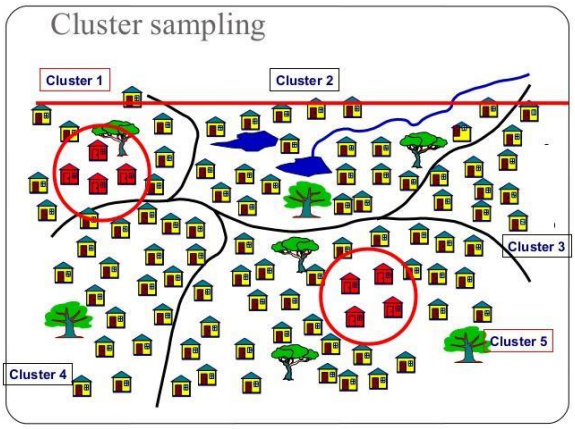

### Stratified Random Sampling

- Used for a heterogeneous population.
- Population is divided into subgroups (strata) based on shared characteristics.



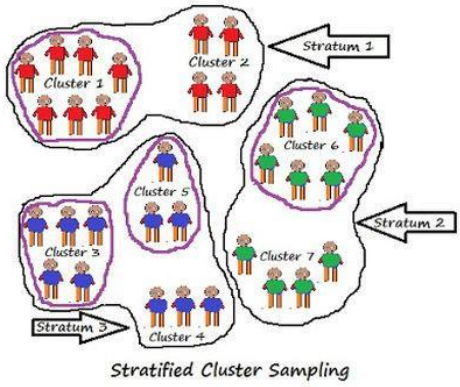
- Sample is selected randomly or systematically from each stratum.
- Ensures better representation of the population.
- Challenges include high cost, effort, and the need for clear subgroup definitions.

## Cluster Sampling




- Used for populations spread over a wide geographical area.
- The population is divided into clusters (e.g., cities, schools, hospitals).
- Entire clusters are randomly selected instead of individual participants.
- Cost-effective and practical for large-scale studies.
- May introduce higher sampling errors compared to other methods.

## Multistage Sampling



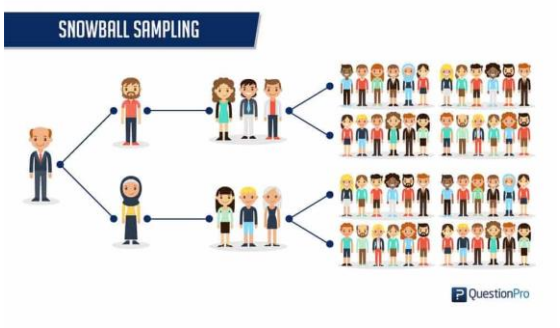

- Combines two or more probability sampling techniques.
- Often involves **Cluster Sampling** followed by **Stratified Sampling** or another method.
- Helps refine the sample selection in large populations.
- Reduces costs and increases efficiency.
- May lead to increased complexity in analysis.

## Non-Probability Sampling

- Not every unit in the population has an equal chance of being selected.
- **Advantages**: Requires less effort, cost, and time.
- **Disadvantages**: Higher risk of sampling errors, bias, and lack of generalizability.

## Non-Probability Sampling Methods

1. **Volunteer Sampling** – Participants self-select to be part of the study.
2. **Convenient Sampling** – Selection based on ease of access to participants.
3. **Purposive Sampling** – Selection based on specific characteristics relevant to the study.
4. **Snowball Sampling** – Existing participants refer new participants.
5. **Matched Sampling** – Participants are selected based on matching characteristics with a control group.
6. **Genealogy-Based Sampling** – Selection based on family lineage or ancestry.


SNOWBALL SAMPLING
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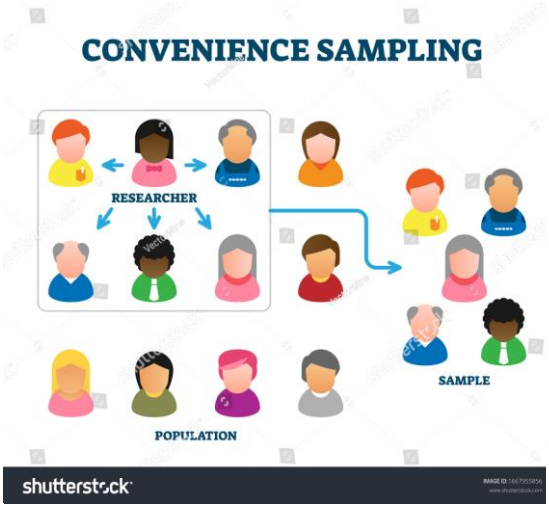
CONVENIENCE SAMPLING
RESEARCHER
SAMPLE
POPULATION
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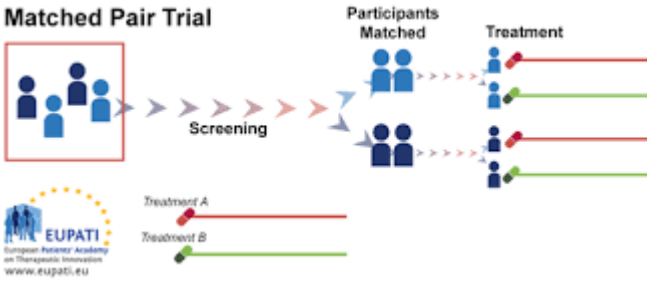
Matched Pair Trial
Participants Matched
Treatment
Screening
EUPATI
Treatment A
Treatment B

# Essential Medicine List

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## Definition of Essential Medicines

Essential medicines are those that satisfy the priority health care needs of the population.

- **23rd edition**: 591 drugs (July 2023)
- **Selection Criteria**:
    - Public health relevance
    - Evidence
    - Efficacy
    - Safety
    - Comparative cost-effectiveness

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## History of Modern Medicines

| Year | Development |
|---|---|
| **1897** | Introduction of Aspirin |
| **1941** | Introduction of Antibiotics |
| **1943** | Introduction of Antimalarials |
| **1944** | Introduction of Antitubercular drugs |
| **1950s** | Oral contraceptives, drugs for diabetes, and mental illness |
| **1977** | WHO Model List of Essential Drugs (208 individual medicines) |

- The WHO list provided **safe and effective treatment** for most communicable and non-communicable diseases.

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## Need for an Essential Medicine List (EML)

| Factors | Explanation |
|---|---|
| List of drugs available in the market | Different prices, different healthcare needs |
| Chances of irrationality | Need a standardized list of medicines |
| Criteria | Safety, efficacy, cost-effectiveness |
| Healthcare coverage | Majority of healthcare needs can be fulfilled |

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## Do We Really Need an Essential Medicine List?

| Reason | Explanation |
|---|---|
| 1. Poor supply chain in LMIC | Limited access in Low- and Middle-Income Countries |
| 2. Cost of Medicines | High prices limit accessibility |
| 3. Availability of Medicines | Ensuring essential drugs are stocked |
| 4. Reducing Mortality | Effective treatment reduces deaths |
| 5. Therapeutic Manuals | Standardized treatment guidelines |
| 6. ADR Monitoring | Adverse Drug Reaction monitoring |
| 7. New Therapeutic Options | Need to include updated medicines |
| 8. Regular Update of EML | Keeping up with medical advancements |
| 9. Resource Constraints | Maximizing benefits in limited settings |

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## Criteria for the Selection of Essential Drugs

| Core List (Basic Health Care) | Complementary List (Specialized Facilities) |
|---|---|
| Minimum drugs required | Specialized treatment options |
| Safe, efficacious, cost-effective | Training requirements |

**Factors for Selection:**

| Criteria | Description |
|---|---|
| 1. Prevalent Disease | Common illnesses requiring treatment |
| 2. Treatment Facilities | Availability of healthcare centers |
| 3. Trained and Experienced Personnel | Skilled medical staff availability |
| 4. Financial Resources | Budget constraints |
| 5. Genetic and Demographic Data | Population-specific treatment needs |
| 6. Scientific Evidence | Backed by research and studies |
| 7. Cost | Affordable options |
| 8. Single Compounds | Preference for individual active ingredients |
| 9. Dosage Form Selection | Suitable forms for different patient needs |
| 10. Quality Assurance | Standardized manufacturing and safety |
| 11. Reserve Anti-Infective Agents | Restricted use of strong antibiotics |

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## Advantages and Uses of the Essential Medicines List (EML)

## Advantages:

1. **Better Healthcare** – Ensures people have access to the most needed medicines.
2. **Affordable Treatment** – Helps keep medicine costs low and affordable.
3. **Quality and Safety** – Includes only safe, effective, and tested medicines.
4. **Guidance for Doctors** – Helps doctors choose the best treatment options.
5. **Prevents Resistance** – Encourages proper use of antibiotics to avoid drug resistance.
6. **Cost-Effective Choices** – Focuses on medicines that offer the best value for money.

7. **Better Control** – Promotes wise use of medicines and reduces misuse.
8. **Regularly Updated** – Keeps up with new medical research and health needs.
9. **Supports NEML** – Provides a global base to help countries create their own National Essential Medicines List.
10. **Helps LMICs** – Acts as a useful guide for low- and middle-income countries.

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**Uses:**

1. **Hospitals & Clinics** – Helps in selecting essential, effective medicines.
2. **Government Policies** – Guides national health programs and medicine supply planning.
3. **Pharmacies** – Ensures the most important medicines are always available.
4. **Health Insurance** – Helps decide which medicines should be covered.
5. **Global Health** – Supports better healthcare access worldwide.

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## AWaRe Classification of Essential Medicines

| Aspect | Details |
|---|---|
| **Introduction** | First introduced in 2017 by the WHO Expert Committee on Selection and Use of Essential Medicines. |
| **Purpose** | Classifies antibiotics in the WHO Model List of Essential Medicines into three categories: Access, Watch, and Reserve. |
| **2019 Update** | Expanded to include all commonly used antibiotics globally, beyond just the WHO Model List. |
| **Advisory Group** | Based on recommendations from the EML Antimicrobials Working Group and WHO Expert Committee. |
| **Reference** | Detailed methodology and evidence are available in the WHO Technical Report Series. |

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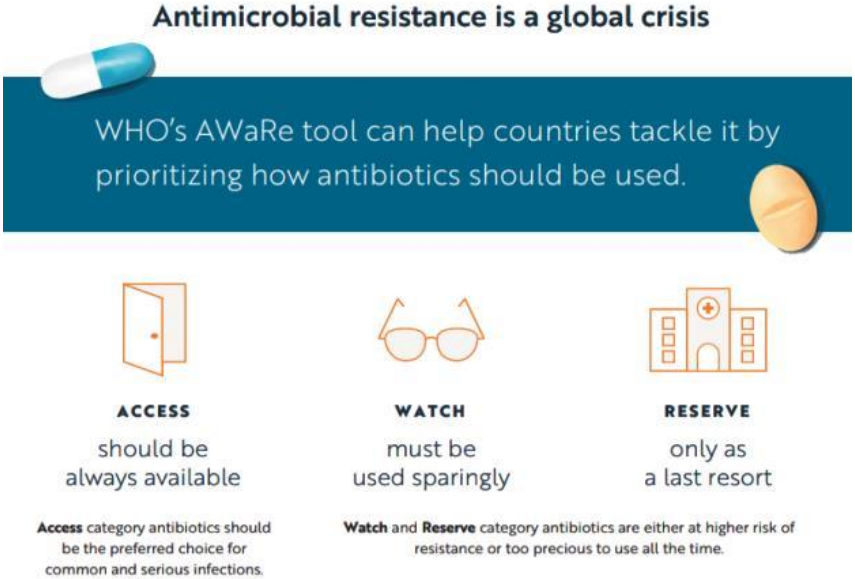
## Prioritizing Antibiotic Use: The WHO AWaRe Tool"



## Advantages and Uses of the Essential Medicines List (EML)

### Advantages:

1. **Better Healthcare** – Ensures people get the most needed medicines.
2. **Affordable Treatment** – Helps keep medicine costs low.
3. **Quality and Safety** – Includes only tested and effective medicines.
4. **Guidance for Doctors** – Helps doctors prescribe the best medicines.
5. **Prevents Resistance** – Promotes proper use of antibiotics to avoid drug resistance.

### Uses:

1. **Hospitals & Clinics** – Helps in choosing essential medicines.
2. **Government Policies** – Guides health programs and medicine supply.
3. **Pharmacies** – Ensures availability of important medicines.
4. **Health Insurance** – Helps decide which medicines to cover.
5. **Global Health** – Supports better medical care in all countries.

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## WHO Expert Committee for EML (23rd Edition)

The WHO Expert Committee for the Essential Medicines List (EML) consists of:

- **15 Committee Members**
- **4 Temporary Advisers**
- **UN Agencies Involved:**
  - UNICEF (United Nations Children's Fund)
  - WHO Regional Heads (5 members from America, South-East Asia, Eastern Mediterranean, etc.)
  - WHO Headquarters in Geneva (Secretariat with 5 members)

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## 23rd Edition of EML (2023) – Updates

- **156 countries** use the WHO EML as a reference.
- **Updated every 2 years** to ensure relevance and effectiveness.
- **Total medicines in the 23rd edition (2023): 502**
- **New additions:** 24 medicines (15 added to the core list, 9 to the complementary list).
- **Review process:**
  - 85 applications considered.
  - 52 applications for adding new drugs.
  - 9 proposals for adding new indications to existing 22 drugs.
  - 9 proposals for new formulations.
  - 6 proposals for removing 13 drugs.
  - 9 applications for other modifications.

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## Symbols Used in EML/23rd Edition of EML Edition:

- **[c] Core List:** Indicates restrictions on use for children.
- **[c] Complementary List:** Requires specialist diagnosis or monitoring.
- □ **(Square Box):** Signifies therapeutic alternatives.
- **Age/Weight Restriction Symbol:** Indicates specific age or weight limits for medicine use.

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## National Essential Medicines List (NEML) 2023

- **Total drugs:** 502
- **First NEML introduced in 1994.**
- Categorized into three levels:
  - **Primary (P)** – Basic healthcare needs.
  - **Secondary (S)** – More specialized healthcare.
  - **Tertiary (T)** – Advanced medical care.

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# DRUG UTILIZATION EVALUATION & DRUG UTILIZATION REVIEW

Chap. 3 Clinical Pharm II
Abuzar Khan PhD

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## Contents



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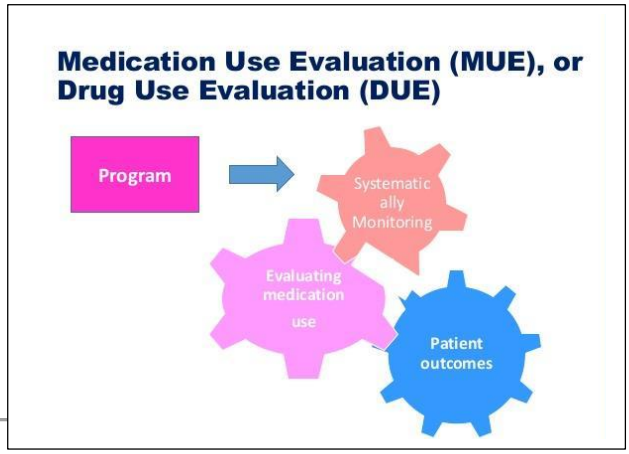
## Drug Utilization Review (DUE)

Also known as:

- MUE
- DUR
- Drug Usage Review

They all have the same meaning.

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## Drug Utilization Evaluation (DUE) Program

- Planned, criteria-based
- Systematic process
- Monitoring, evaluating, and continually improving medication use
- **Aim:** Improving medication-related outcomes for a group of patients or consumers

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## DUE Introduction

**Main Focus Areas:**

- Patient assessment and Patient education.
- Prescribing
- Preparation and dispensing
- Administration
- Patient monitoring for medication safety and efficacy

## DUE vs. Drug Audit

**Drug Audit:**

- Single evaluation focusing on a particular medication, drug class, disease state, or process
- Data collection, organization, analysis, and reporting
- Small component of DUE

**Drug Regimen Review:**

- Review of an individual patient's medication regimen
- Reviewing the appropriateness of a new prescription
- Pharmacist's personal judgement. rather than explicit criteria

**Pharmaceutical Care:**

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## DUE Definition

- ***Formal Program*** Assesses data on drug ***use against*** explicit, prospective standards and ***introducing curative strategies*** as necessary to achieve desired outcomes.
- **Corrective Actions:** Introduces **Indicators:**
    - **Red Flags** – Warning signs in drug utilization.
    - **Quantitative Measures** – Objective assessment tools.
    - **Example:** Postoperative infection rate.

## Importance of DUE

- Improves medication use.
- Ensures proper formulary management.
- Reports adverse drug reactions.
- Prevents medication errors.
- Enhances pharmacist involvement.
- Supports clinical pharmacy services.

## Role of Pharmacist

- **Responsibility** – Ensures proper medication use.
- **Interdisciplinary Approach** – Collaborates with healthcare professionals.
- **Team Involvement** – Works with physicians, prescribers, nurses, administrators, and patients.
- **Leadership** – Pharmacist should take the lead in medication management.

## Goals of DUE

1. **Effectiveness:** Ensuring optimal therapeutic outcomes
2. **Efficiency:** Reducing unnecessary medication use
3. **Medication Safety:** Preventing adverse drug reactions
4. **Patient Satisfaction:** Enhancing treatment experience
5. **Cost Reduction:** Minimizing unnecessary expenses
6. **Optimizing Care:** Improving overall healthcare delivery

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## Scope of DUE

1. **High-Risk Medications:** Anticoagulants, chemotherapy, immunosuppressants
2. **High-Use/High-Volume Medications:** Common antibiotics, chronic disease medications
3. **High-Cost Medications:** Expensive drugs and procedures
4. **Drugs Used in High-Risk Patient Groups:** Critically ill, elderly, neonates
5. **Problem-Prone Drugs:** Medications frequently associated with safety concerns

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## Types of DUE

1. **Retrospective Review:** Evaluating past medication use.
2. **Prospective Review:** Assessing medication before it is prescribed
3. **Concurrent Review:** Monitoring drug use in real time

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## PART-II (PRACTICE)

## Practice Case: Surgery DUE

- **Issue:** Postoperative infection rates for abdominal surgeries were higher than the national average.
- **Observation:** The pharmacy director noticed frequent use of cefoxitin, which was costly and inappropriate.
- **Decision:** The committee initiated a Drug Utilization Review (DUR) for antibiotic prophylaxis in abdominal surgery wound infections.
- **Justification:** The health problem met all DUR criteria – high use, high cost, high risk, and problem-prone.

## Priority of Problem:

| Medication/health problem | High use | High cost | High risk | Problem prone | Total score |
|---|---|---|---|---|---|
| Paracetamol | 1 | 0 | 0 | 0 | 1 |
| Acute respiratory infections | 2 | 0 | 1 | 1 | 4 |
| Ceftriaxone | 1 | 2 | 0 | 0.5 | 3.5 |
| Warfarin | 0.5 | 0 | 1 | 2 | 3.5 |
| H2 antagonists | 1 | 1 | 0 | 1 | 3 |
| Surgical antimicrobial prophylaxis | 1 | 1.5 | 0.5 | 1 | 4 |

* Each medicine or health problem is rated 0–2 on the basis of the use, risk, cost, and probability of problems. The highest total scores may be targeted for the DUR.

## Steps in DUE

| Step | Description |
|---|---|
| **Step 1** | Establish responsibility by forming a DUE committee |
| **Step 2** | Develop scope and identify priority medications |
| **Step 3** | Establish criteria and standards based on evidence-based guidelines |
| **Step 4** | Collect and analyze data using surveys and software tools |
| **Step 5** | Identify and analyze medication-related problems |
| **Step 6** | Implement corrective actions and interventions |
| **Step 7** | Monitor outcomes and ensure adherence |

---

## Steps in DUE

### Step I: Establish Responsibility

- Form a hospital committee.
- Plan activities and procedures.
- Distribute tasks and responsibilities.

### Step II: Develop Scope

- Identify medication use problems.
- Prioritize:
  - High-volume medicines.
  - Medicines with a low therapeutic index.
  - Medicines with a high incidence of ADRs.
  - Expensive medicines.

## Step III: Establish Criteria

- **Sources:**
  - Based on literature.
  - Reviewed by local and international experts.
  - Standard Treatment Guidelines (STG) must be accepted by medical staff.

- **Developing Thresholds:**
  - Pharmacy administration indicators:
    - Correct cost to patient
    - Accurate billing records
    - Accurate dispensing records
    - Appropriate use of generic medicines or therapeutic equivalents
    - Appropriate use of formulary medicines
    - Appropriate quantity dispensed

### Step IV: Data Collection and Results

- **Types of Data Collection:**
  - Prospective, retrospective, and concurrent methods.
- **Tools Used:**
  - Questionnaires, PDAs, chart reviews, computerized software systems.
- **Presentation of Results:**
  - Graphical or descriptive formats.

## Step V: Analysis

- **Frequency of Analysis:**
  - Conducted quarterly or annually.
- **Methods:**
  - Data tabulation.
  - Statistical analysis.
- **Intervention:**
  - If thresholds are not met, it may indicate a medicine use problem requiring DTC (Drug and Therapeutics Committee) attention.

### Step VI: Action Plan

- Fix medicine use problems.
- DTC decides to continue, stop, or expand DUE.

## Step VII: Follow-up

- Ensure issues are resolved through regular checks.

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### Problems / Challenges in DUE

1. **Lack of Authority:** Insufficient enforcement power
2. **Poor Prioritization:** Ineffective selection of key drugs/issues
3. **Inadequate Follow-Up:** Lack of sustained monitoring
4. **Poor Documentation:** Incomplete record-keeping affects reliability

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## Practical Case Study: Surgery DUE

**Issue:** High postoperative infection rates in abdominal surgeries
**Findings:**

- Surgeons used non-recommended antibiotics
- Delayed preoperative antibiotic doses
- Overprescription of high-dose antibiotics
- Unnecessary use of antibiotics for certain surgeries

**Priority of the Problem:** High use, high cost, high risk, and problem-prone

| Criterion | Benchmark (%) | Indicator: % Compliance per quarter | | | |
|---|---|---|---|---|---|
| | | 1st | 2nd | 3rd | 4th |
| 1. Antibiotic selection (per *Medical Letter*) | 100 | 70 | 85 | 94 | 100 |
| 2. Correct dose (per *Medical Letter*) | 95 | 65 | 90 | 94 | 97 |
| 3. Preoperative dose 0–2 hours before surgery | 95 | 30 | 52 | 89 | 94 |
| 4. Postoperative dose only for dirty surgery | 98 | 78 | 89 | 82 | 91 |
| 5. No postoperative infection | 96 | 90 | 93 | 96 | 100 |
| 6. No adverse reactions to medicines | 97 | 97 | 100 | 87 | 97 |

| Review Criteria from DTC | Patients | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| Indications[a] | Tonsillitis | Otitis media | Urethritis | Bowel sterilization | Severe gram-negative meningitis | Boils/ abscess | Severe cystitis | Surgical prophylaxis | Pneumonia | Severe wound infection |
| Appropriate indication? | Yes | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Yes |
| Amoxicilline dosage[b] | 250 mg tds | 250 mg tds | 250 mg tds | 1,500 mg bd | 500 mg tds | 250 mg tds | 500 mg tds | 250 mg tds | 250 mg tds | 500 mg tds |
| Duration (usually 5 days) | 5 days | 7 days | 7 days | 1 day | 10 days | 7 days | 5 days | 5 days | 5 days | 7 days |
| Cost per capsule (KES) | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| Total cost[c] | 470 | 650 | 650 | 380 | 1,800 | 650 | 920 | 470 | 470 | 1,280 |

**Table 1. Sample DUE Criteria for Ciprofloxacin**

| Indicator | Criteria | Threshold, % |
|---|---|---|
| Indication | Complicated, chronic, or relapsing urinary tract infection (UTI)<br>Gonorrhea<br>Resistant respiratory tract infections<br>Bone and joint infections<br>Prostatitis<br>Gastrointestinal (GI) infections | 90 |
| Dose | Complicated or recurrent infections: 500–750 mg bid<br>GI infections: 500 mg bid<br>Gonorrhea: 250 mg in 1 dose<br>Dose in renal disease decrease as follows:<br>Creatinine clearance (CrCl) 30–50 ml/min<br>– 250–500 q 12 h 5–29 ml/min<br>– 250–500 q 18 h<br>Hemodialysis—500 mg q 24 h | 95 |
| Duration | Complicated UTI: 10–21 days<br>Respiratory: 7–14 days<br>Osteomyelitis: 4–6 weeks<br>GI infection: 5 days | 95 |
| Contraindications | Pregnancy<br>Children younger than 18 | 100 |
| Medicine interactions | Medicines—theophylline, antacids, iron, sucralfate, probenecid<br>Food: decreased absorption with milk | 90 |
| Outcome | Negative cultures<br>Improved symptomatology<br>No treatment failures | 90 |

**Annex 1. Example of Established DUE Criteria on Data Collection Form for Amikacin**

**Date:** **Medicine: AMIKACIN** **Data collector's initials:** _____

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Patient Chart No.** | | | | | | | |
| **Diagnosis** | | | | | | | |
| **Age/Sex/Weight** | | | | | | | |
| **Date Treated** | | | | | | | |
| **Criteria and Indicators** | **Threshold** | **Observed** | | | | | |
| Justification for medicine being prescribed | | | | | | | |
| 1. Serious infections caused by susceptible strains of aerobic gram-negative bacteria resistant to gentamicin and tobramycin | 95% | | Yes No | Yes No | Yes No | Yes No | Yes No |
| 2. Suspected serious gram-negative infections acquired in the hospital with high resistance rates to gentamicin and tobramycin | 95% | | Yes No | Yes No | Yes No | Yes No | Yes No |
| 3. In combination with an antipseudomonal penicillin when treating serious pseudomonas infections | 95% | | Yes No | Yes No | Yes No | Yes No | Yes No |
| Process criteria | | | | | | | |
| 4. Obtain serum creatinine before therapy or within 24 hours of initiation of therapy | 100% | | Yes No | Yes No | Yes No | Yes No | Yes No |
| 5. Loading dose of 7.5 mg/kg (IV or IM) based on ideal body weight | 100% | | Yes No | Yes No | Yes No | Yes No | Yes No |
| 6. Maintenance dosage range of 15 mg/kg/day ideal weight (exception: renal compromise) | 100% | | Yes No | Yes No | Yes No | Yes No | Yes No |
| 7. Therapy changed to tobramycin, gentamicin, or other medicine if culture and sensitivity indicate less expensive or more appropriate medicine | 100% | | Yes No | Yes No | Yes No | Yes No | Yes No |
| Outcome criteria | | | | | | | |
| 8. Clinical improvement noted in patient medical records | 90% | | Yes No | Yes No | Yes No | Yes No | Yes No |
| 9. Fever reduction to normal within 72 hours | 90% | | Yes No | Yes No | Yes No | Yes No | Yes No |

# Therapeutic Drug Monitoring

## Introduction

Therapeutic Drug Monitoring (TDM) is the practice of individualizing drug dosages by maintaining plasma or blood concentrations within a target range to achieve optimal therapeutic effects while minimizing toxicity.

### Definition

- **CPR**: A practice applied to a specific group of drugs to target particular drug levels, ensuring a safer and more effective clinical response than clinical assessment alone.
- **Collat**: A routine practice for certain drugs where clinical response is compared to drug therapy.
- **Pk-Made Easy**: TDM ensures individualized dosage regimens by maintaining serum drug concentrations (SDC) within a therapeutic window using pharmacokinetic (Pk) parameters:
    - Absorption
    - Steady-state concentration
    - Volume of distribution
    - Clearance
    - Elimination
    - Plasma level-time curve
    - Half-life (T ½)

### Therapeutic Range

Therapeutic range is the blood concentration range where a drug is most effective with minimal toxicity.

**Key Concepts:**

- At lower concentrations, both therapeutic effects and toxicity are minimal.
- As drug concentration increases, therapeutic effects rise until they stabilize.
- Toxicity risk increases gradually but becomes significant beyond a certain concentration.
- Some patients may experience toxicity within the therapeutic range, while others tolerate higher concentrations without adverse effects.
- Most drugs are monitored at **steady-state**, meaning equilibrium exists between blood and tissue concentrations.
- A decrease in blood drug concentration results in a proportional decrease in tissue concentrations, including at the drug's site of action.

## Aims and Objectives: TDM aims to:

- Optimize and personalize patient responses to drug therapy.
- Maintain **serum drug concentration** within a safe and effective range.
- Prevent drug-induced toxicity from excessive concentrations.
- Avoid therapeutic failure from insufficient concentrations.

### Therapeutic Ranges of Common Drugs

| Drug | Therapeutic Range (mg/L) | Drug | Therapeutic Range (mg/L) |
|---|---|---|---|
| Digoxin | 0.5 - 2.0 | Carbamazepine | 5 – 12 |
| Amiodarone | 1.0 - 2.5 | Sodium Valproate | 50 – 100 |
| Theophylline | 10 – 20 | Phenobarbital | 15 – 40 |

## Common Candidates for TDM

TDM is commonly applied to the following drugs:

- **Cardiac Drugs**: Digoxin, Amiodarone, Quinidine, Perhexiline
- **Anti-epileptic Drugs**: Carbamazepine, Sodium Valproate, Phenobarbital, Phenytoin
- **Antibiotics**: Gentamicin, Tobramycin, Netilmicin, Amikacin, Vancomycin
- **Bronchodilators**: Theophylline
- **Psychotropic Drugs**: Amitriptyline, Imipramine, Nortriptyline
- **Local Anesthetics**: Lidocaine, Mexiletine
- **Salicylates**: Aspirin derivatives

# General Procedure for the Determination of Pharmacokinetic (Pk) Parameters

Therapeutic Drug Monitoring (TDM) involves optimizing and individualizing drug therapy through the application of key **pharmacokinetic (Pk) parameters**, which include:

### Key Pk Parameters

- **AUC (Area Under the Curve)** – Measures total drug exposure over time.
- **Onset Time** – The time it takes for the drug to start showing effects.
- **Duration of Action** – The time for which the drug remains effective.
- **Intensity** – The magnitude of the drug's effect.
- **$C_p$ max (Maximum Plasma Concentration)** – The peak drug concentration in blood.
- **$T_m$ax (Time to Reach $C_p$ max)** – Time taken to reach peak concentration.
- **MEC (Minimum Effective Concentration)** – The lowest concentration needed for a therapeutic effect.
- **MTC (Minimum Toxic Concentration)** – The lowest concentration at which toxicity begins.

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# Qualitative vs. Quantitative Drug Studies

**Past Approach:**

- Pharmacologists evaluated drug **availability** based on **clinical response** only.
- Example: In **anti-hypertensive drugs**, they monitored **blood pressure (BP)** changes qualitatively.

**Modern Approach:**

- Advanced analytical methods allow for **quantitative drug measurement**, including the detection of **parent compounds and metabolites** in biological samples.
- This has improved drug monitoring accuracy and effectiveness.

## Analytical Techniques Used for Drug Measurement

| Technique | Description |
|---|---|
| **HPLC (High-Performance Liquid Chromatography)** | Separates and quantifies drug components. |
| **LCMS (Liquid Chromatography-Mass Spectrometry)** | Provides precise drug concentration analysis. |
| **Immunoassay (e.g., ELISA, FPIA)** | Detects specific drug molecules using antibodies. |
| **Gas Chromatography** | Identifies drug compounds in gaseous form. |
| **Spectrophotometry** | Measures drug concentration based on light absorption. |
| **Radioisotopic Methods** | Uses radioactive markers to detect drugs. |

## Factors Influencing the Choice of Analytical Method

- **Physicochemical properties of the drug** (e.g., solubility, stability).
- **Target concentration to be measured** (therapeutic vs. toxic levels).
- **Nature of the biological specimen** (e.g., **blood, serum, urine**).
- **Availability of instruments and trained personnel**.
- **Cost and accessibility of the assay method**.

Due to **cost and equipment limitations**, most clinical pharmacokinetic services use **immunoassays**, such as:

- **Abbott Therapeutic Drug System**
- **Fluorescence Polarization Immunoassay (FPIA)** – Used for anti-arrhythmics, aminoglycosides, and drugs of abuse testing.

### Commercial Drug Testing Kits

Some companies provide **pre-made kits** for drug testing:

- **Syntex**
- **Eastman Kodak**
- **Hoffman-La Roche**
- **Miles Laboratories**

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# When to Take Blood Samples for Pk Analysis?

Before measuring drug concentration, practitioners must determine **whether drug level monitoring is necessary**.

**Why?**

- Some adverse effects (**e.g., nausea, allergies**) are unrelated to drug concentration.
- Monitoring should be based on **therapeutic relevance**, not just side effects.

### Blood Sampling Times for TDM

- **During the post-distribution phase** (for a **loading dose**).
- **At steady-state** (for a **maintenance dose**).

### Example: Blood Sampling for Pk Analysis

1. **Multiple samples** are collected over time.
2. A **drug concentration vs. time** graph is plotted.
3. The **AUC (Area Under the Curve)** is calculated to assess drug exposure.

# Therapeutic Window and Therapeutic Index in Therapeutic Drug Monitoring (TDM)

# 1. Therapeutic Window / Index

The **Therapeutic Index (TI)** is the ratio of:

Therapeutic Index=MTCMEC\text{Therapeutic Index} = \frac{\text{MTC}}{\text{MEC}}

- **MTC (Minimum Toxic Concentration):** The lowest concentration at which toxicity occurs.
- **MEC (Minimum Effective Concentration):** The lowest concentration required for therapeutic effect.

A **narrow therapeutic index (NTI)** means the drug must be carefully monitored to **avoid toxicity while maintaining efficacy**.

---

# 2. Key Pharmacokinetic Parameters in Drug Therapy

### Onset Time

- The **time required** for the drug to reach **MEC** and begin its pharmacological action.

### Duration of Action

- The period during which the drug maintains an **effective concentration** in the blood.

### Intensity of Drug Effect

- Determined by **the number of receptors occupied** by the drug.
- **Higher drug concentration → Higher intensity of effect**, but also **higher risk of toxicity**.
- Example: **Phenytoin**
  - **Therapeutic Range: 10-20 mg/L**
  - **> 20 mg/L → Nystagmus** (involuntary eye movements).
  - **30-40 mg/L → Ataxia** (lack of muscle coordination).
  - **> 40 mg/L → Mental changes** (confusion, lethargy).
- The **Therapeutic Range** is the drug concentration range where **maximum therapeutic effect occurs with minimal adverse effects**.

---

# 3. Significance of Therapeutic Drug Monitoring (TDM)

1. **Rapid Achievement of Proper Dosage**
   - Crucial in **emergency situations** (e.g., accidents, surgery, anesthesia).
2. **Evaluation of Existing Dosing Regimens**
   - Ensures that drug levels are **adequate** for therapeutic effects.
3. **Prevention of Drug Toxicity**
   - Helps maintain drug levels **within the therapeutic range**, reducing **empirical dosing errors**.
4. **Differentiation Between Pharmacokinetic (PK) and Pharmacodynamic (PD) Failure**
   - **PK Failure:** Drug does **not reach** sufficient blood levels.
   - **PD Failure:** Drug reaches the bloodstream but does **not elicit the desired effect** (e.g., receptor resistance).
5. **Cost-Effectiveness**
   - Though expensive initially, TDM reduces:
     - **Toxicity rates**
     - **Hospitalization duration**
     - **Complications**
     - **Overall healthcare costs**
6. **Measurement of Drug Bioavailability (BA)**
   - Determines:
     - **Absolute Bioavailability** (fraction reaching systemic circulation).
     - **Relative Bioavailability** (comparison with a reference formulation).

7. **Application in Dose-Response Studies**
    - Helps in determining **individualized dosage regimens**.
8. **Plasma Half-Life Calculation**
    - Determines **drug elimination rate**, helping in dosing adjustments.
9. **Evaluation of Drug-Drug Interactions**
    - Identifies metabolic changes due to **co-administered drugs**.
10. **Determination of Dose-Related Adverse Drug Reactions (ADRs)**
    - Assesses **augmented ADRs** to optimize therapy.
11. **Calculation of Optimal Dosage for Individuals**
    - Ensures **personalized treatment** for each patient.
12. **Bioequivalence Studies**
    - Compares different formulations of the **same drug**.
13. **Estimation of Drug Accumulation**
    - Determines potential buildup of **active parent drug or metabolites**.
14. **Study of Receptor Sensitivity**
    - Helps understand **variations in drug response** among patients.
15. **Prediction of Drug Levels in Biological Fluids**
    - Determines drug presence in **blood, urine, and tissues** with various dosing regimens.

---

# 4. Criteria for TDM Candidate Drugs

Drugs requiring **TDM** typically have:

1. **Narrow Therapeutic Index (NTI)**
    - **Precise monitoring** is needed to prevent **toxicity or sub-therapeutic effects**.
2. **High Pharmacokinetic Variability**
    - Differences in absorption, metabolism, and clearance among individuals.
3. **Non-Linear Pharmacokinetics**
    - **Dose adjustments** are unpredictable due to **enzyme saturation**.
    - Example: **Phenytoin, Salicylates, Alcohols**
4. **Steep Dose-Response Curve**
    - A **small increase in dose** leads to **significant changes** in drug effect.
5. **Major Dose-Related Side Effects**
    - Example: **Phenytoin**
        - **> 20 mg/L → Nystagmus**
        - **30-40 mg/L → Ataxia**
        - **> 40 mg/L → Mental impairment**
6. **Specific Pharmacokinetic Considerations**
    - **Plasma Protein Binding**
        - Example: **Phenytoin** is **highly protein-bound**.
        - In **hypoalbuminemia**, more **free drug** is available → **higher toxicity risk**.
    - **Active Metabolites**
        - Some drugs produce **active metabolites** that require monitoring:
            - **Carbamazepine** → Carbamazepine-10,11-epoxide
            - **Procainamide** → N-acetyl procainamide
            - **Theophylline** → Caffeine

        - **Imipramine** → Desipramine
7. **Drug Intolerance**
    - **TDM is less effective** in drugs with rapid **tolerance development** (e.g., opioids).
8. **Reversibility**
    - Drugs must be **reversible** in action (i.e., their effects should **decrease** when dosage is reduced).
    - Example of **Irreversible Drugs** (TDM **not effective**):
        - **Alkylating anticancer agents**
        - **Phenoxybenzamine** (α-blocker)
9. **Availability of Drug Assay Technology**
    - Requires:
        - **Sensitive and accurate methods** (e.g., HPLC, LC-MS).
        - **Rapid analysis** of **parent drug, active metabolites, and enantiomers**.
10. **Sound Clinical Judgment**
    - Requires **trained healthcare professionals** with knowledge of:
        - **Pharmacokinetics**
        - **Drug metabolism**
        - **Signs of toxicity**
    - Example: **Digoxin (0.9-2.0 mg/L)**
        - **Hypokalemia** increases **Digoxin toxicity**, so **TDM is crucial**.

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**Blood Sampling and Therapeutic Drug Monitoring (TDM)**

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# 1. Blood Sampling

## 1.1 Importance of Blood Sampling in TDM

- Blood plasma or serum is usually used for drug assays, depending on the equipment.
- The most critical step in sampling is using the correct tube to avoid interference.
- Incorrect sampling times can lead to misleading plasma drug concentrations:
    - **Early sampling (absorption or distribution phase)** → Incorrect plasma drug levels (↑ or ↓).
    - **Best sampling time** → During the **elimination phase** for accurate results.

## 1.2 Recommended Blood Sampling Times *(Schumacher, 1958)*

| Dose Type | Recommended Sampling Time |
|---|---|
| **Loading Dose** | Post-distribution/Elimination phase |
| **Maintenance Dose** | At Steady State |

- In some cases, **whole blood** is used instead of plasma (e.g., **cyclosporine**).

- Some blood collection tubes with gels can interfere with drug levels and should be replaced.

---

# 2. Usual Sampling Time

- **Correct sampling time is crucial** because drug concentration varies throughout the dosing interval.
- Clinical pharmacists may need to advise on when to collect blood samples.
- **Multiple vs. Single Sampling:**
  - **Aminoglycosides** → Multiple blood samples at specific times.
  - **Digoxin & Phenytoin** → Single sample at **steady state**.

## 2.1 Factors Affecting Sampling Time

| Factor | Variations |
|---|---|
| **Drug Formulation** | Solid, Semi-solid, Liquid |
| **Route of Administration** | Oral, Parenteral |
| **Dosage Schedule** | OD, BD, TDS |
| **Duration of Therapy** | Short-term, Long-term |

---

# 3. Therapeutic Drug Monitoring (TDM)

## 3.1 Definition

- TDM helps individualize drug doses by maintaining plasma/blood concentrations within a **therapeutic range (therapeutic window).**
- **Sources of Variability in Drug Response:**
  - **Pharmacokinetic Variability** → Differences in drug absorption, distribution, metabolism, and excretion.
  - **Pharmacodynamic Variability** → Differences in drug effect at receptor sites.

## 3.2 Major Sources of Pharmacokinetic Variability

| Source | Examples |
|---|---|
| **Patient Compliance** | Adherence to dosing regimen |
| **Age** | Neonates, children, elderly |
| **Physiology** | Gender, pregnancy |
| **Disease States** | Hepatic, renal, cardiovascular, respiratory disorders |
| **Drug Interactions** | Effects on metabolism, absorption |
| **Environmental Factors** | Influence on drug metabolism |
| **Genetic Polymorphisms** | Differences in metabolic enzymes |

---

# 4. Drugs Suitable for TDM

- **Characteristics of drugs requiring TDM:**
  - **High pharmacokinetic variability**
  - **Therapeutic & adverse effects depend on drug concentration**
  - **Narrow therapeutic index**
  - **Well-defined therapeutic range**
  - **Difficult-to-monitor therapeutic effects**
- TDM is especially important when:
  1. **Drugs are used prophylactically** (e.g., for seizures, arrhythmias, asthma, organ rejection).
  2. **Drugs have a narrow therapeutic range** (e.g., aminoglycoside antibiotics).

## 4.1 Commonly Monitored Drugs & Therapeutic Ranges

| Drug | Therapeutic Range (mg/L) | Drug | Therapeutic Range (mg/L) |
|---|---|---|---|
| **Digoxin** | 1.0-2.5 | **Carbamazepine** | 5-12 |
| **Amiodarone** | 2.0-5.0 | **Sodium Valproate** | 50-100 |
| **Lidocaine** | 2.0-5.0 | **Phenobarbitone** | 15-40 |
| **Quinidine** | 2.0-5.0 | **Gentamicin, Tobramycin, Netilmicin** | Trough <2; Peak >5 |
| **Flecainide** | 0.2-0.9 | | |
| **Mexilitine** | 0.5-2.5 | **Amikacin** | Trough <5; Peak >15 |
| **Salicylate** | 150-300 | | |
| **Perhexiline** | 0.15-0.6 | **Vancomycin** | Trough <10; Peak 20-40 |
| **Theophylline** | 10-20 | | |
| **Phenytoin** | 10-20 | **Lithium** | 0.5-1.0 mmol/L |

---

# 5. Sampling and Drug Analysis

## 5.1 Assay Methods

- **Key requirements:**
  - **Sensitive** enough to detect small drug concentrations.
  - **Specific** to the drug/metabolite.
  - **Accurate and precise.**
- **Common Drug Assay Methods:**
  - **Automated Immunoassay (widely used)**
  - **Manual Assay (for complex drugs):**
    - **High-Performance Liquid Chromatography (HPLC)**
    - **Gas Liquid Chromatography (GLC)**

## 5.2 Sample Collection

- Plasma or serum is commonly used.
- **Whole blood** is used for drugs like **cyclosporine** due to shifts between red cells and plasma.
- **Blood collection tubes** with separation gels can interfere with drug levels.

## 5.3 Timing of Samples

- **Drug concentrations fluctuate** over the dosing interval.
- **Pre-dose (trough levels)** are the most stable.
- **For short half-life drugs** → Collect **pre-dose samples**.
- **For long half-life drugs** (e.g., **phenytoin, amiodarone**) → Timing is flexible.
- **For digoxin** → Collect samples **6+ hours post-dose**.

## 5.4 Information Required for Interpretation

| Factor | Importance |
|---|---|
| **Time of Sampling** | Helps determine steady state levels |
| **Duration of Treatment** | Indicates accumulation trends |
| **Dosing Schedule** | Affects plasma concentration |
| **Patient Information** | Age, gender, disease conditions |
| **Other Medications** | Drug interactions |
| **Reason for Test** | Toxicity, routine monitoring, lack of effect |

## 5.5 Factors Affecting Interpretation

### 1. Changes in Protein Binding

- **Plasma assays measure total drug (bound + unbound),** but only the unbound drug is active.
- If protein binding changes (e.g., due to **renal disease**), **total drug concentration does not reflect true activity**.
    - Example: **Phenytoin** (Therapeutic range **10-20 mg/L**)
        - If **fraction unbound increases** (e.g., **renal disease**), the actual therapeutic range shifts to **5-10 mg/L**.

### 2. Active Metabolites

- Some metabolites contribute to drug activity but are **not measured in assays**.
- **Examples:**
    - **Carbamazepine** → Metabolized to an active form (**Carbamazepine-10,11-epoxide**).
    - **Procainamide** → Metabolized to **N-acetylprocainamide**.
    - **Neonatal Theophylline** → Converted to **Caffeine** (requires different therapeutic range).

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# Clinical Pharmacokinetics and Therapeutic Drug Monitoring (TDM)

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## 1. Clinical Pharmacokinetics (P.K)

### 1.1 Definition

Clinical pharmacokinetics is a discipline that applies pharmacokinetic principles to optimize drug therapy by designing individualized dosage regimens. It ensures therapeutic effectiveness while minimizing adverse drug reactions.

### 1.2 Uses of Clinical Pharmacokinetics

| Purpose | Description |
|---|---|
| **Dose Optimization** | Determines the appropriate drug dose for an individual. |
| **Dosing Interval** | Establishes the correct timing for drug administration. |
| **Bioequivalence Evaluation** | Assesses differences in drug formulation absorption. |
| **Drug Level Prediction** | Estimates drug concentration in plasma, tissues, and urine. |
| **Accumulation Estimation** | Predicts drug/metabolite build-up over time. |
| **Drug Interaction Analysis** | Identifies and explains drug-drug interactions. |
| **Toxicity Diagnosis** | Helps detect overdose-related toxicity. |
| **Patient Monitoring** | Identifies incorrect doses, adverse reactions, and non-compliance. |

### 1.3 Role of Clinical Pharmacokinetics in Pharmaceutical Care

- Ensures correct drug dosing and administration.
- Monitors drug therapy to prevent toxicity.
- Evaluates patient responses for unexpected effects.
- Educates healthcare professionals on pharmacokinetic principles.
- Recommends drug assays to improve therapy.

---

## 2. Pharmacist's Role in Clinical Pharmacokinetic Monitoring

| Responsibility | Description |
|---|---|
| **Dosage Design** | Creates personalized drug regimens based on patient factors. |
| **Monitoring & Adjustments** | Modifies dosages based on drug concentration in biological fluids. |
| **Explaining Drug Response** | Investigates unusual patient reactions to drugs. |

| Responsibility | Description |
|---|---|
| **Communication** | Shares pharmacokinetic information with physicians and nurses. |
| **Education & Training** | Trains healthcare professionals on clinical pharmacokinetics. |
| **Recommending Drug Assays** | Suggests lab tests for accurate drug concentration measurement. |
| **Quality Assurance** | Documents patient outcomes and economic benefits of monitoring. |

---

# 3. Therapeutic Drug Monitoring (TDM)

## 3.1 Definition

TDM involves measuring drug concentrations in the blood at specific intervals to maintain a **constant and effective** level of medication while minimizing toxicity.

## 3.2 Clinical Applications of TDM

| Application | Benefit |
|---|---|
| **Treatment Optimization** | Helps ensure a patient responds appropriately to a drug. |
| **Non-Compliance Detection** | Differentiates between non-compliance and true non-response. |
| **Monitoring Individual Variability** | Adjusts dosage based on patient-specific factors. |
| **Toxicity Confirmation** | Determines if symptoms are drug-induced. |
| **Dosage Verification** | Ensures patients receive adequate drug levels. |
| **Drug Interaction Identification** | Detects and prevents harmful interactions. |
| **Altered Drug Disposition** | Adjusts doses for patients with disease-related changes in drug metabolism. |

---

# 4. Concept of TDM

- TDM is based on the principle that for certain drugs, **plasma drug concentration is directly related to therapeutic and toxic effects**.
- If a **clear concentration-effect relationship does not exist**, TDM is unnecessary.
- Plasma drug level measurement is only justified when it improves therapeutic outcomes.

### 4.1 Criteria for Appropriate TDM

| Criteria | Requirement |
|---|---|
| **Narrow Therapeutic Range** | The drug has a small margin between effective and toxic doses. |
| **Plasma Level-Effect Relationship** | Drug effects correlate with plasma concentrations. |
| **Difficult-to-Monitor Therapeutic Effect** | Clinical response is hard to assess without TDM. |
| **High Variability in Drug Response** | Large differences exist in drug metabolism among individuals. |
| **Available Analytical Techniques** | Reliable methods exist for measuring drug/metabolite levels. |

### 4.2 When TDM is Unnecessary

| Situation | Reason |
|---|---|
| **No Dose-Concentration Relationship** | Plasma levels do not predict effectiveness/toxicity. |
| **Standard Dosing is Effective** | No need for individualized monitoring. |
| **Clinical Effects are Measurable** | Outcomes can be observed without blood tests. |
| **Wide Therapeutic Range** | Low risk of toxicity (e.g., beta-blockers, calcium channel blockers). |

---

# 5. Narrow Therapeutic Index Drugs

These drugs require TDM due to their **small margin between therapeutic and toxic doses**.

| Category | Drugs |
|---|---|
| **Antiepileptics** | Phenytoin, Carbamazepine, Valproic Acid, Phenobarbital, Primidone |
| **Antimicrobials** | Gentamicin, Amikacin, Vancomycin |
| **Cardiovascular Drugs** | Digoxin |
| **Immunosuppressants** | Cyclosporine |
| **Bronchodilators** | Theophylline |
| **Mood Stabilizers** | Lithium |

---

# 6. Factors Affecting TDM Interpretation

## 6.1 Key Pharmacokinetic Factors

| Factor | Impact on Drug Levels |
|---|---|
| **Absorption** | Affects how much drug reaches the bloodstream. |
| **Volume of Distribution** | Determines drug distribution in tissues vs. blood. |
| **Elimination & Half-Life** | Influences drug clearance and accumulation. |
| **Sampling Time** | Timing affects measured drug levels. |
| **Therapeutic Range** | Helps assess whether the drug is effective or toxic. |

---

# 7. Sampling Time in TDM

## 7.1 Importance of Correct Sampling Time

- Ensures **accurate interpretation** of drug levels.
- **Incorrect sampling times** can lead to misleading results and inappropriate dose adjustments.

## 7.2 Steady-State Concentration

- Steady-state occurs when the **rate of drug administration = rate of elimination**.
- It typically takes **4-5 half-lives** to reach steady-state.

**Half-Lives % of Steady-State Achieved**

| | | |
|---|---|---|
| **1** 50% | **3** 87.5% | **5** 96.88% |
| **2** 75% | **4** 93.75% | **6** 98.44% |

## 7.3 Sampling Guidelines for Different Drugs

| Drug | Trough Sampling Time | Peak Sampling Time |
|---|---|---|
| **Aminoglycosides (e.g., Gentamicin, Amikacin)** | Immediately before next dose | 30 min after IV infusion |
| **Digoxin, Lithium, Cyclosporine** | During elimination phase | Not applicable |

- **For drugs with a long half-life (e.g., Phenobarbital):** Fluctuations in concentration are minimal, making trough sampling sufficient.
- **For drugs with a short half-life (e.g., Gentamicin):** Both **peak and trough levels** are crucial.

---

## 8. Therapeutic Ranges in TDM

- Therapeutic ranges **guide dose adjustments** but should not be taken as absolute.
- Some patients may require **higher or lower levels** to achieve the desired response.
- **Therapeutic range + Clinical response** = **Optimal dose determination**.

---

# Practical/Clinical Pharmacokinetics (CPK)

Clinical Pharmacokinetics (CPK) is the application of pharmacokinetic principles in humans to design individualized dosage regimens that optimize the therapeutic response of medications while minimizing adverse drug reactions (ADRs).

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## 1. Important Uses of Pharmacokinetics

The main uses of pharmacokinetic principles in optimizing drug therapy are:

| Purpose | Description |
|---|---|
| **Optimal Dose Determination** | Determining how much drug should be given to an individual patient. |
| **Dosing Interval** | Identifying the most appropriate time to administer the dose. |
| **Bioequivalence Evaluation** | Assessing differences in physiological availability between formulations. |

### Other Uses

- Predicting drug levels in plasma, tissues, and urine.
- Estimating drug/metabolite accumulation.
- Explaining pharmacokinetic drug interactions.
- Diagnosing drug toxicity due to overdose.

---

## 2. Clinical Pharmacokinetics in Pharmaceutical Care

CPK helps identify and resolve potential problems in patients who are:

- Taking the wrong dose of the correct drug.

- Experiencing ADRs.
- Experiencing drug-drug or drug-food interactions.
- Non-compliant with their medication regimen.
- Receiving drugs with a narrow therapeutic index (TDM).

---

## 3. Pharmacist's Role in Clinical Pharmacokinetic Monitoring

| Role | Description |
|---|---|
| **Designing Drug Dosage Regimens** | Creating patient-specific dosage plans based on pharmacokinetics and clinical conditions. |
| **Monitoring & Adjusting Dosage** | Modifying drug regimens based on pharmacologic response and drug concentration in biological fluids. |
| **Evaluating Unusual Responses** | Investigating unexpected patient responses for possible pharmacokinetic explanations. |
| **Communicating with Healthcare Team** | Providing pharmacokinetic insights to physicians, nurses, and clinical practitioners. |
| **Educating Healthcare Professionals** | Training pharmacists, doctors, and nurses on pharmacokinetic principles and TDM. |
| **Recommending Drug Assays** | Advising on appropriate tests for drug concentration analysis. |
| **Developing Quality Assurance Programs** | Documenting improved patient outcomes and economic benefits of pharmacokinetic monitoring. |

---

# Therapeutic Drug Monitoring (TDM)

TDM is the measurement of blood drug concentration at intervals to maintain a relatively constant level of medication in the bloodstream. It is used to individualize drug dosage by maintaining plasma or blood drug concentration within a target therapeutic range.

## Clinical Usefulness of TDM

| Application | Description |
|---|---|
| **Better Insight into Drug Response** | Helps distinguish between non-compliance and true non-response to medication. |
| **Individualized Drug Utilization** | Accounts for variations in drug metabolism due to physiological or disease states. |
| **Reduced ADRs** | Patients monitored via TDM suffer fewer adverse reactions. |
| **Shorter Hospitalization** | Leads to shorter hospital stays. |

| Application | Description |
|---|---|
| **Improved Disease Control** | Studies show better control in epilepsy patients when TDM is used. |
| **Monitoring Compliance** | Ensures patients are taking their medication correctly. |
| **Confirming Drug Toxicity** | Determines if toxicity symptoms are due to excessive drug levels. |
| **Adjusting Drug Dosage** | Ensures plasma concentration is within the therapeutic range. |
| **Evaluating Drug Interactions** | Identifies possible drug-drug interactions affecting drug levels. |

---

# 4. Basic Concepts of TDM

## When is TDM Necessary?

TDM is useful when:

1. The drug has a **narrow therapeutic index**.
2. A **direct relationship** exists between plasma drug levels and therapeutic/toxic effects.
3. **Therapeutic effects cannot be clinically observed directly**.
4. There is **large individual variability** in drug metabolism.
5. **Reliable analytical techniques** are available to measure drug concentrations.

## When is TDM Unnecessary?

TDM is **not needed** when:

1. The drug has a **wide therapeutic index** (e.g., beta-blockers, calcium channel blockers).
2. Clinical outcome is **not related to plasma concentration**.
3. Dosage does not require individualization.
4. The **drug effect can be clinically measured** without lab tests.

---

# 5. Drugs with a Narrow Therapeutic Index (NTI)

| Drug Class | Examples |
|---|---|
| **Antiepileptics** | Phenytoin, Valproic Acid, Carbamazepine, Phenobarbital, Primidone |
| **Antimicrobials** | Vancomycin, Aminoglycosides (Gentamicin, Amikacin) |
| **Cardiovascular (CVS)** | Digoxin |
| **Immunosuppressants** | Cyclosporine |

| Drug Class | Examples |
|---|---|
| **Bronchodilators** | Theophylline |
| **Mood Stabilizers** | Lithium |

---

# 6. Factors Affecting TDM Interpretation

1. **Absorption** – Rate and extent of drug absorption.
2. **Volume of Distribution (Vd)** – Drug distribution in body fluids.
3. **Elimination & Half-life (t1/2)** – How fast the drug is removed from the body.
4. **Sampling Time (ST)** – When the blood sample is taken relative to the last dose.
5. **Therapeutic Ranges** – Target plasma drug levels for efficacy and safety.

---

# 7. Sampling Time (ST) in TDM

Correct sampling time is **critical** for accurate interpretation of TDM data.

| Sampling Type | Best Time for Blood Sample Collection |
|---|---|
| **Trough Level** | Immediately before the next dose. |
| **Peak Level** | 30 minutes after a 30-minute IV infusion ends, 15 minutes after a 60-minute IV infusion ends. |

## Importance of Sampling Time

- If blood samples are taken **too soon** after dosing, drug concentration appears falsely **elevated**, leading to potential **under-dosing**.
- If taken **too late**, the levels may appear **lower**, leading to potential **over-dosing**.
- **Steady-state (SS) concentration** is achieved when the drug input (dosing) equals drug elimination.
- SS is typically reached after **4–5 half-lives**.

## Steady-State Drug Concentration Over Time

| No. of Half-Lives | % of Steady-State Achieved | No. of Half-Lives | % of Steady-State Achieved |
|---|---|---|---|
| 1 | 50% | 4 | 93.75% |
| 2 | 75% | 5 | 96.875% |
| 3 | 87.5% | | |

---

# 8. Therapeutic Ranges

Therapeutic ranges serve as a **guideline** for optimum drug concentrations but should not be considered absolute because:

- Some patients may respond to drug levels above or below the recommended range.
- Some may experience **toxic effects** even within the "therapeutic" range.
- **Therapeutic range + clinical response = appropriate dose determination**.

---

**THERAPEUTIC RANGE**

- Used as a guide to achieving optimal drug concentration.
- Should not be considered absolute because:
  - Some patients may respond to levels above or below the range.
  - Some may experience toxicity within the therapeutic range.
- Dose determination should always consider:
  - **Therapeutic range**
  - **Clinical response**
  - **Individualized dosing**

---

## Drugs with Low Therapeutic Index & TDM of Gentamicin

- **Aminoglycosides** (Amikacin, Gentamicin, Tobramycin) are bactericidal and active against:
  - Some **Gram-positive** organisms
  - Many **Gram-negative** organisms (e.g., *Pseudomonas aeruginosa*)

### Factors Affecting Dose and Dosage Regimen

- Causative agent
- Renal function
- Concurrent disease state
- Patient’s weight

---

## Adverse Effects & Risk Factors

- **Main adverse effects:** Nephrotoxicity & Ototoxicity (dose-related)
- **Risk factors:**
  - Older patients
  - Renal dysfunction
  - Previous aminoglycoside use
  - Liver disease
  - High daily doses
  - Prolonged treatment
  - Short dosing intervals
  - Co-administration with nephrotoxic drugs

---

### Therapeutic Ranges

| Parameter | Multiple Daily Dosing | Once Daily Dosing |
|---|---|---|
| **Peak** | 5-12 mg/L | Varies |
| **Trough** | <2 mg/L | Varies |

*(TDM values depend on pharmacokinetics)*

---

### Pharmacokinetic Properties

| Property | Details |
|---|---|
| **Absorption** | Poorly absorbed from GIT; administered via **IV infusion (30-60 min)** or **IM injection** |
| **Distribution** | Volume of distribution (Vd) = **0.25 L/kg**; mainly confined to extracellular fluids |
| **Elimination** | 85-95% excreted unchanged in urine; half-life **1.5-4 hrs** (normal renal function) |
| **Steady-State** | Achieved in **7.5-20 hrs** |

- **Follows a two-compartment model**: Distribution phase completes within **1 hour** (sampling considerations).
- **Elimination requires ~5 half-lives (7.5-20 hrs)** in normal renal function.

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Here's your organized and structured document with tables for better readability. I have kept the original text intact while simplifying difficult terms where necessary.

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# FACTORS AFFECTING PLASMA CONCENTRATION

## 1) Gentamicin

### Factors Affecting Plasma Concentration

| Factor | Effect |
|---|---|
| **Diseases** | |
| Dehydration | Decreased Volume of Distribution (Vd) |
| Burn patients | Decreased Vd |
| Obesity | Increased Vd |
| Renal impairment | Decreased clearance |
| Congestive Cardiac Failure (CCF) | Decreased clearance |

| Factor | Effect |
|---|---|
| Fever | Increased clearance |
| **Drugs** | Carbenicillin & Ticarcillin may inactivate Gentamicin. |

### Usual Sampling Time

- **Trough Level:** Immediately before the next dose.
- **Peak Level:**
  - 30 min after a **30 min IV infusion**
  - 15 min after a **60 min IV infusion**

### Practical Implications

- **Initial Dosage:** Based on physiological parameters (e.g., clearance, elimination).
- **Changing Dosage:**
  - Not simple as changing the dose affects both **peak and trough levels**.
  - Requires blood level measurement and pharmacokinetic (PK) equations to adjust dosage.
- **Once Daily Dosing (ODD):**
  - Beneficial due to **concentration-dependent bacterial killing**.
  - **Long post-antibiotic effect** and less nephrotoxicity.
  - **Not recommended** in children, pregnant/breastfeeding women, burn patients, renal failure.
- **Dose:** 5-7 mg/day (if creatinine clearance > 60 ml/min).
- **Blood Sample Collection:** 6-14 hrs after the 1st dose, then adjusted based on levels.

---

# 2) Digoxin

### Clinical Uses

- **Increases** the force of heart contractions.
- **Reduces** conduction within the atrioventricular (AV) node.
- **Used for:**
  - Supraventricular tachycardias.
  - Controlling ventricular response in **atrial fibrillation**.

### Adverse Effects & Risk Factors

- Effects depend on:
  - Plasma concentration of the drug.
  - Heart's sensitivity, which increases in heart disease.
- **Toxicity is not solely predicted by plasma concentration**—clinical effects are more important.
- **Heart rate monitoring** is crucial in atrial fibrillation patients.
- Regular monitoring **not necessary** unless issues arise.

## Serum Concentration & Response Relationship

| Concentration (µg/mL) | Response |
|---|---|
| <0.5 | No clinical effect |
| 0.7 | Some positive inotropic & conduction-blocking effect |
| 0.8 – 2 | **Optimum therapeutic range** |
| 2 - 2.5 | Increased risk of toxicity |
| >2.5 | **Gastrointestinal (GI), Cardiovascular (CVS), and Central Nervous System (CNS) toxicity** |

## Pharmacokinetic Properties

| Property | Details |
|---|---|
| **Absorption** | Poor, variable (~60-70% in tablet form) |
| **Distribution** | Vd = 7.3 L/kg (widely distributed in tissues) |
| **Elimination** | **60-80% renal excretion (unchanged)**, 20-40% hepatic metabolism |
| **Half-life (t½)** | **40 hrs** (normal renal function), **120 hrs** (renal impairment) |
| **Steady-state concentration** | 5-7 days (normal renal function), longer in renal impairment |

## Usual Sampling Time

- **6 hrs after administration**

## Factors Affecting Plasma Concentration

| Factor | Effect |
|---|---|
| **Decreased Absorption** | Antacids, Malabsorption |
| **Decreased Clearance** | Verapamil, Amiodarone, Spironolactone, Quinidine, Renal & Hepatic Impairment, CCF |
| **Increased Concentration** | Hypothyroidism (decreased metabolism & renal excretion) |
| **Decreased Concentration** | Hyperthyroidism |
| **Increased Heart Sensitivity** | Hypokalemia, Hypercalcemia |

## Practical Implications

- **Population values (normal PK values) help estimate plasma concentration**, but individuals vary.
- **Therapeutic Drug Monitoring (TDM)** helps optimize dosage and reduce adverse effects.

- Diseases and drugs significantly impact digoxin's pharmacokinetics.

---

# 3) Theophylline

## Clinical Use

- Used for **bronchial asthma**.

## Adverse Effects

- **Cardiovascular:** Tachycardia, palpitations, arrhythmias.
- **Gastrointestinal (GI):** Nausea, vomiting.
- **Central Nervous System (CNS):** Headache, insomnia, seizures (if given too rapidly).

## Serum Concentration & Response Relationship

| Concentration (mg/L) | Response |
|---|---|
| <5 | No significant bronchodilation |
| 5 – 10 | Some bronchodilation |
| 10 – 20 | **Optimum therapeutic range** |
| 20 – 30 | Increased risk of nausea, vomiting, cardiac arrhythmias |
| >30 | **Severe cardiac arrhythmias** |

## Pharmacokinetic Properties

| Property | Details |
|---|---|
| **Absorption** | 100% after oral administration |
| **Distribution** | Vd = 0.5 L/kg (widely distributed, **does not distribute well in fat**) |
| **Elimination** | **>90% hepatic metabolism**, <10% renal excretion (unchanged) |
| **Half-life (t½)** | 6 - 12 hrs |
| **Steady-state concentration** | 1.5 - 2.5 days (chronic dosing) |

## Product Formulation

- **Aminophylline** (the ethylenediamine salt of theophylline) is **80% theophylline** (salt factor = 0.8).
- **Sustained-release (SR) preparations** vary in bioavailability.
- **Lower absorption rate constant (Ka) = better slow-release properties**.

### Usual Sampling Time

- **Trough Level:** Immediately before the next dose.
- **Peak Level:** 4-7 hrs after oral SR preparation (depends on formulation).

### Factors Affecting Plasma Concentration

| Factor | Effect |
|---|---|
| **Decreased Clearance** | Cimetidine, Allopurinol, Cor Pulmonale, Hepatic Dysfunction, Acute Pulmonary Edema |

### Practical Implications

- **IV bolus doses should be given slowly (preferably as a short infusion)** to prevent adverse effects.
- **Dosage must be individualized based on plasma concentration** due to variable hepatic metabolism.
- **Liver diseases and drug interactions can significantly affect theophylline metabolism.**

---

# 4)Phenytoin

## Clinical Use

- Anti-epileptic

## Adverse Effects

- **20-30 mg/L**: Nystagmus, blurred vision
- **>30 mg/L**: Ataxia, dysarthria (motor speech disorder), drowsiness, coma

## Serum Concentration & Response Relationship

| Concentration (mg/L) | Response |
|---|---|
| <5 | No therapeutic effect |
| 5-10 | Some anticonvulsant activity |
| 10-20 | Optimum therapeutic range |
| 20-30 | Nystagmus, blurred vision |
| >30 | Ataxia, dysarthria, drowsiness, coma |

## Pharmacokinetic Properties

| Property | Details |
|---|---|
| **Absorption** | 80-95% after oral administration |
| **Distribution** | Vd = 1 L/kg, 90% protein-bound, two-compartment model |
| **Elimination** | >95% hepatic metabolism, <5% renal excretion (unchanged) |
| **Half-life (t½)** | 30-100 hrs (not a useful parameter due to non-linear kinetics) |
| **Steady-state concentration** | 7-14 days before sampling (range: 8-30 days) |

## Usual Sampling Time

- **Trough Level**: Immediately before the next dose

## Factors Affecting Plasma Concentration

| Factor | Effect |
|---|---|
| **Decreased Clearance** | Cimetidine, Isoniazid, Barbiturates (high conc.), Chronic liver disease |
| **Increased Clearance** | Carbamazepine, Alcohol, Barbiturates (low conc.), Acute hepatitis |
| **Protein Binding** | Hypoalbuminemia increases free drug levels |

## Practical Implications

- Narrow therapeutic index.
- Non-linear dose-concentration relationship.
- Small dosage increases may cause large plasma concentration changes and toxicity.
- Monitoring plasma concentration is essential for dosage adjustment.

---

# 5)Carbamazepine

## Clinical Use

- Drug of choice for **simple and complex partial seizures**.
- Also used for **tonic-clonic seizures**.
- Drug of choice for **trigeminal neuralgia**.

## Serum Concentration & Response Relationship

| Concentration (mg/L) | Response |
|---|---|
| <4 | Little therapeutic benefit |
| 4-12 | Optimum range (monotherapy) |
| 4-9 | Optimum range (with other anti-convulsants) |

| Concentration (mg/L) | Response |
|---|---|
| >9 | Nystagmus, diplopia (double vision), drowsiness, ataxia (lack of coordination) |
| >12 | Ataxia, dysarthria, drowsiness, coma (even in monotherapy) |

# Pharmacokinetic Properties

| Property | Details |
|---|---|
| **Absorption** | Slow and variable (bioavailability: 75-85%) |
| **Distribution** | Widely distributed, highest in liver and kidneys, 70-90% protein bound, Vd = 0.8-2 L/kg |
| **Elimination** | >98% hepatic metabolism, <2% renal excretion (unchanged) |
| **Auto-induction** | Begins within first few days of therapy |
| **Half-life (t½)** | Up to 35 hrs (single dose), decreases to 5-7 hrs (regular dosing) |
| **Steady-state concentration** | 2-4 weeks after starting therapy |

# Usual Sampling Time

- **Trough Level**: Measured immediately before the next dose.

# Factors Affecting Plasma Concentration

| Factor | Effect |
|---|---|
| **Inhibition of metabolism** | Cimetidine, Isoniazid, Clarithromycin, Ketoconazole, Verapamil, Diltiazem |
| **Induction of metabolism** | Phenytoin, Barbiturates |

# Practical Implications

- Limited use of pharmacokinetic equations due to auto-induction.
- Drug interactions (e.g., Phenytoin) significantly affect metabolism and blood levels.
- Each 100 mg dose increases plasma concentration at steady state by **1 mg/L** in adults.

---

# 6) Phenobarbitone

### Clinical Use

- Generalized tonic-clonic epilepsy
- Partial seizures

### Serum Concentration & Response Relationship

| Concentration (mg/L) | Response |
|---|---|
| <15 | Little therapeutic effect |
| 15-40 | Optimum therapeutic range |
| 40-50 | Sedation, confusion in elderly |
| >60 | Ataxia, lethargy, stupor, coma |

### Pharmacokinetics

| Property | Details |
|---|---|
| **Absorption** | 70-90% after oral administration |
| **Distribution** | Vd = 0.7-1 L/kg, 50% protein bound |
| **Elimination** | 50-80% hepatic metabolism, 20-50% renal excretion |
| **Half-life (t½)** | 53-140 hours |
| **Steady-State Concentration** | 2-4 weeks |

### Usual Sampling Time

- **Any time at steady state (due to long half-life)**

### Factors Affecting Plasma Concentration

| Decrease Clearance | Increase Concentration |
|---|---|
| Hepatic impairment | Methylphenidate |
| Renal impairment | - |

### Practical Implications

- Affected by liver/kidney disease but **not** by other antiepileptics
- Periodic plasma monitoring useful for dose adjustments

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# 7) Vancomycin

### Clinical Use

- **Pseudomembranous colitis**
- **Severe staphylococcal infections** (resistant strains)
- **Endocarditis** (with aminoglycosides)

### Serum Concentration & Toxicity

| Parameter | Value (mg/L) |
|---|---|
| Desired Peak | 25-40 |
| Desired Trough | 5-10 |
| Toxic Concentration | >80 |
| Ototoxicity Risk | 80-100 |
| Nephrotoxicity Risk | ↑ **risk with high serum levels** |

### Pharmacokinetics

| Property | Details |
|---|---|
| **Absorption** | Poor oral absorption, given IV |
| **Distribution** | Vd = 0.5-1.0 L/kg |
| **Elimination** | 80-90% renal excretion |
| **Half-life (t½)** | 5-11 hrs (renal impairment → prolonged) |
| **Steady-State Concentration** | 2 days (sampling on day 3) |

### Usual Sampling Time

- **Peak:** 1 hour after 1-hour infusion
- **Trough:** Immediately before next dose

### Factors Affecting Toxicity

- ↓ **Clearance:** Renal impairment
- ↑ **Toxicity:** Concurrent ototoxic/nephrotoxic drugs (aminoglycosides)

### Practical Implications

- **Monitoring needed in:**
  - Renal impairment
  - Long-duration/high-dose therapy
  - Severe infections (endocarditis, meningitis)
  - High-risk patients (pregnant, burn victims, IV drug abusers)

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# 8) Lithium (Li)

## Clinical Uses

- **Mood stabilizer** used in **bipolar disorder** (both treatment and prophylaxis).

# Serum Concentration & Response Relationship

| Serum Concentration (mmol/L) | Response |
|---|---|
| <0.4 | Little therapeutic effect |
| 0.4 – 1.0 | Optimum range for prophylaxis |
| 0.8 – 1.2 | Risk of renal impairment, ataxia, weakness, drowsiness, thirst, diarrhea |
| 3 – 5 | Confusion, spasticity, dehydration, convulsions, coma, death |
| >3.5 | Medical emergency |

# Pharmacokinetic Properties (PK)

| Property | Details |
|---|---|
| **Absorption** | Variable in rate and extent |
| **Distribution** | Unevenly distributed throughout the body |
| **Volume of Distribution (Vd)** | 0.5 – 1 L/kg |
| **Model** | Follows a two-compartment model |
| **Distribution Time** | ~8 hours (so steady-state sampling at 12 hours) |
| **Elimination** | 90 – 98% renal excretion (unchanged drug), minor excretion via feces (1%) and sweat (4 – 55%) |
| **Diurnal Variation in Clearance** | Slower at night than during the day |
| **Elimination Half-Life (t½)** | 8 – 35 hours (average ~18 hours) |
| **Time to Steady-State Concentration** | Achieved after a few days of chronic dosing |

# Usual Sampling Time

- **12 hours after the evening dose**

# Factors Affecting Plasma Concentration

| Decrease Clearance (↑ Lithium Levels) | Increase Clearance (↓ Lithium Levels) |
|---|---|
| Renal impairment | Aminophylline |
| Dehydration | - |
| Diuretics (especially thiazides) | - |
| ACE inhibitors | - |
| NSAIDs (except Aspirin) | - |

# Practical Implications

- **Dosage adjustments** lead to **proportional changes** in blood levels.
- **Monitoring is essential** before prescribing lithium.
- **Conversion Factors for Different Lithium Salts:**

| Lithium Salt | Lithium Ion Equivalent |
|---|---|
| 100 mg Lithium carbonate | 2.7 mmol $Li^+$ |
| 100 mg Lithium citrate | 1.1 mmol $Li^+$ |

# PHARMACEUTICAL CARE, ITS SCOPE, MANAGEMENT AND APPLICATION OF CARE PLAN

**Chapter 5 – Clinical Pharmacy II**

*By Abuzar Khan, PhD*

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PHARMACEUTICAL CARE Summary

1. **Assessment**
2. **Care Plan**
3. **Evaluation**

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## Contents



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## Case History

- **Patient Name:** Jamal Khan
- **Address:** Peshawar
- **Gender:** Male
- **Age:** 47 years
- **Height:** 65 inches
- **Weight:** 185 lbs
- **Allergies:** Aspirin
- **Diagnosis:** Asthma
- **Other Information:** Smoker

*Drugs:*

1. **Tab. Theophylline** 300 mg BD
2. **Albuterol** 2 puffs every 4 hours or as needed

*Chief Complaint (CC):*

- Cough, shortness of breath (SOB)
- Frequent exacerbation requiring MDI weekly
- Poor quality of life (QOL)
- **PEFR** between 60-80% of personal best

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## Patient Healthcare

1. **Patient Care**
2. **Medical Care**
3. **Pharmaceutical Care**
4. **Nursing Care**

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## Pharmaceutical Care

- Appropriate use of medicines
- Avoid irrational use of medicines
- **Pharmacists' Role:**
    - Educate patients on safe drug use
    - Guide on diet and lifestyle
    - Maximize safe and effective medication use

*Definition of Pharmaceutical Care*

- **Coined by Mikeal et al. (1975):**
  *"The care that is given, patient requires, and receives, which assures safe and rational drug use."*
- **Hepler and Strand's Definition:**
  *"Pharmaceutical care is the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve the patient's quality of life."*

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## Pharmaceutical Care Process (PCP)

- **Involves:**
    - Prescription analysis
    - Identifying drug-related problems (DRPs)
    - Consulting prescribers and patients to resolve issues

*Historical Development:*

- **Early 20th Century:** Apothecary
- **1960s:** Dispenser
- **Late 1990s:** Pharmaceutical Care

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## Focus Areas of Pharmaceutical Care

- All patients, including those with:
  - Diabetes Mellitus (DM)
  - Hypertension (HTN)
  - Asthma
  - Chronic Kidney Disease (CKD)
  - AIDS
  - Polypharmacy

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## Pharmaceutical Care Settings

- Hospitals
- Community pharmacies
- Nursing homes
- Home-based care services
- Clinics
- Other medicine-prescribing locations

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## Pharmaceutical Care Activities

- Medical history review
- Drug information
- Prescribing advice
- Patient education and counseling
- Adverse drug reactions (ADRs) and toxicity monitoring
- Drug interactions (DIs) management
- Dosage adjustments for renal & hepatic impairment
- Compliance monitoring
- Lab monitoring
- Therapeutic Drug Monitoring (TDM)
- Cost-related activities

## Scope/Goals of Pharmaceutical Care

1. Cure of the patient's disease
2. Reduce or eliminate disease symptoms
3. Arrest or slow disease progression
4. Prevent diseases or symptoms

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Pharmaceutical Care Plan (PCP)

- **Definition:**
  - An individualized, comprehensive medication therapy plan developed for each patient. Based on clearly defined therapeutic goals Regularly revised according to patient needs.
  - A plan developed by clinical pharmacist for individual patient; evaluated and revised according to the changing needs of the patient on continuous basis; for the purpose to formalize, optimize and document a specific course of treatment.

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Developing a Pharmaceutical Care Plan

## 1. Gathering Information

- Medical history
- Lab tests
- Hospitalization records
- Significant events during drug therapy

## 2. Identifying Problems

- Subjective (S)
- Objective (O)
- Drug-Related Problems (DRPs)

---

## Drug Therapy Problems

1. **Need for additional drug therapy:** Patient has a medical condition that requires initiation of new or additional drug therapy.
2. **Unnecessary drug therapy:** Patient is taking drug therapy that is not needed given their present medical condition.

3. **Wrong drug:** Patient has medical problem treated with therapy that is less effective, more costly, or more hazardous than alternative therapies.
4. **Dose too low:** Patient is taking correct drug for medical condition, but too little of drug is being taken.
5. **Adverse drug reaction:** Patient has medical problem caused by an adverse drug effect, which may include a side effect as well as an allergic reaction; idiosyncratic reaction; and a drug–drug, drug–food, or drug–laboratory test interaction.
6. **Dose too high:** Patient is taking correct drug for medical condition, but too much of drug is being taken.
7. **Nonadherence:** Patient has medical problem resulting from not taking or receiving drug prescribed.

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## 3. Assessing Problems

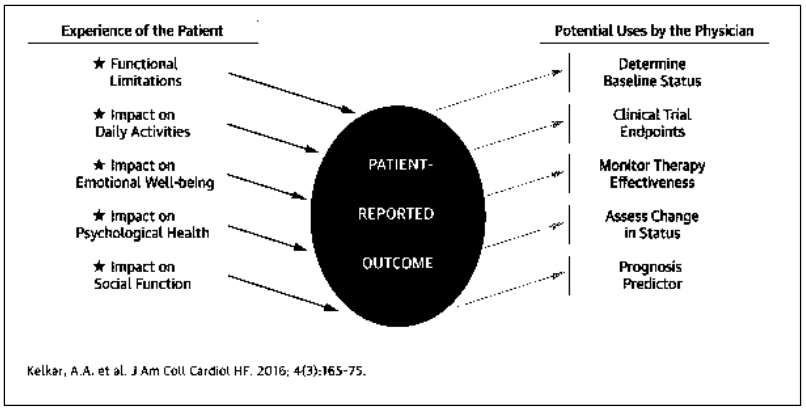
- Integration of subjective and objective data
- Conclusion

## 4. Plan Development

- Goals linked to patient's problem
- Course of action
- Must positively impact overall patient health

## 5. Outcomes Evaluation

- **Outcomes should be:**
  - Meaningful
  - Measurable
  - Manageable
  - Have measurable indicators




## 6. Monitor and Follow-up

- Regular assessment and adjustments

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SOAP Method in Pharmaceutical Care

## Subjective Data (S):

- Information provided by the patient or a caregiver
- Obtained via interview
- Includes patient history and past events

- **Mnemonic: OLDCHARTS**

## Objective Data (O):

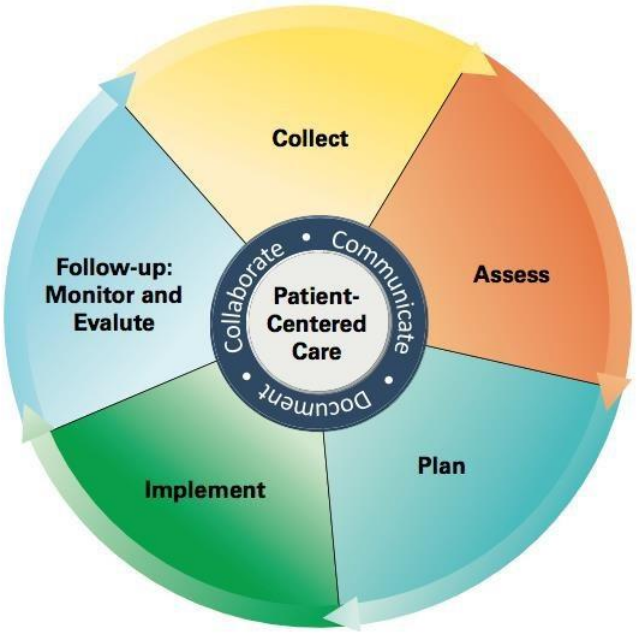
- Information observed or measured by the practitioner
- Includes:
    - Weight, height, blood pressure, pulse
    - Physical exam findings
    - Lab test results
    - Medication records from pharmacy or hospital
- Measurable and reproducible

## Assessment (A):

- Evaluation of subjective and objective findings

## Plan (P):

- Based on S/O findings & final assessment of each problem
- **Includes:**
    - Desired outcomes/goals
    - Recommendations/interventions
    - Monitoring plan for each DRP
    - Future patient education initiatives




**Pharmacists' Patient Care Process**

Pharmacists use a patient-centered approach in collaboration with other providers on the health care team to optimize patient health and medication outcomes.

**Using principles of evidence-based practice, pharmacists:**

**Collect**
The pharmacist assures the collection of the necessary subjective and objective information about the patient in order to understand the relevant medical/medication history and clinical status of the patient.

**Assess**
The pharmacist assesses the information collected and analyzes the clinical effects of the patient's therapy in the context of the patient's overall health goals in order to identify and prioritize problems and achieve optimal care.

**Plan**
The pharmacist develops an individualized patient-centered care plan, in collaboration with other health care professionals and the patient or caregiver that is evidence-based and cost-effective.

**Implement**
The pharmacist implements the care plan in collaboration with other health care professionals and the patient or caregiver.

**Follow-up: Monitor and Evaluate**
The pharmacist monitors and evaluates the effectiveness of the care plan and modifies the plan in collaboration with other health care professionals and the patient or caregiver as needed.

# Pharmaceutical Care – Scope, Management & Application

## 1. Overview of Pharmaceutical Care

Pharmaceutical care involves **assessing, planning, and evaluating** patient treatment to improve health outcomes. It includes managing chronic diseases like **asthma** and **heart failure** through personalized care plans.

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## 2. Developing a Pharmaceutical Care Plan (PCP)

### Key Steps

1. **Gather Information** – Collect patient history and current medications.
2. **Identify Problems** – Recognize health concerns affecting treatment.
3. **Assess Problems** – Determine causes of poor health outcomes.
4. **Plan** – Develop strategies to improve patient adherence.
5. **Evaluate Outcomes** – Monitor improvements and make adjustments.

---

## 3. Case Study 1: Asthma Management

### Patient Information

| Detail | Description |
|---|---|
| **Name** | Jamal Khan |
| **Gender** | Male |
| **Age** | 47 years |
| **Height** | 65 inches (5’5”) |
| **Weight** | 185 lbs |
| **Allergies** | Aspirin |
| **Diagnosis** | Asthma |
| **Smoking** | Yes |
| **Medications** | Theophylline 300 mg BD, Albuterol (2 puffs every 4 hrs or as needed) |

### Identified Problems

- **Chief Complaints (CC):** Chronic cough, shortness of breath (SOB), frequent asthma attacks.
- **Quality of Life (QOL):** Poor, requiring frequent medication use.
- **Peak Expiratory Flow Rate (PEFR):** 60–80% of personal best.

### Assessment

- Poor asthma control due to:
  - Smoking
  - Obesity
  - Non-adherence to medication
  - Inadequate anti-inflammatory treatment

### Pharmaceutical Care Plan

| Problem | Intervention |
|---|---|
| **Smoking** | Refer to smoking cessation program |
| **Obesity** | Refer to dietitian for weight management |
| **Non-Compliance** | Check medication calendar and refill reminders |
| **Cough/SOB** | Suggest adding inhaled corticosteroid |

### Evaluation

| Issue | Action Plan | Evaluation Criteria |
|---|---|---|
| **Smoking** | Smoking cessation referral | Assess improvement in cough & SOB |
| **Obesity** | Dietitian consultation | Check weight reduction progress |
| **Non-Compliance** | Medication refill reminders | Review refill history and inhaler use |
| **Cough/SOB** | Pulmonologist consultation | Monitor PEFR (>80% of personal best) |

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# 4. Case Study 2: Heart Failure Management

### Patient Information

| Detail | Description |
|---|---|
| **Gender** | Male |
| **Age** | 61 years |
| **Location** | Peshawar |
| **Smoking** | Heavy smoker |
| **Medical History** | Diabetes (DM), Hypertension (HTN) for 10 years |
| **Diagnosis** | Heart Failure (HFC) |
| **Symptoms** | SOB, Fatigue, Cough, Difficulty Walking |

## Clinical Findings

| Parameter | Value | | | | |
|---|---|---|---|---|---|
| **BP** | 150/90 mmHg | **Serum Creatinine** | 2 mg/dl (elevated) | **Ankle Edema** | Present |
| **JVP** | 8 cm of water | **Urine** | Protein present | **Chest Crackles** | Present |
| **RBS** | 200 mg/dl (high) | | | | |

## Diagnostic Tests

| Test | Findings |
|---|---|
| **ECG** | Left Ventricular Hypertrophy (LVH), ST and T wave changes (suggesting infarction) |
| **ECHO** | Ejection Fraction (EF) = 33%, Left Ventricular dilation, Left atrial enlargement |

## Medications

| Drug | Dosage | | | | |
|---|---|---|---|---|---|
| Digoxin | 0.25 mg (every other day) | Enalapril | 5 mg BD | Naproxen | 500 mg BD |
| Furosemide | 40 mg BD | Nitroglycerin (Sublingual) | 0.4 mg SOS | | |
| Isosorbide Dinitrate | 20 mg TDS | Amitriptyline | 25 mg OD (night) | | |

## Identified Problems & Care Plan

| Problem | Assessment | Intervention | Evaluation |
|---|---|---|---|
| **Fatigue, SOB, Cough** | Heart failure-related symptoms | Refer for diet assessment & lifestyle changes | Monitor improvement |
| **Noncompliance (Diet)** | Poor diet management (salt intake) | Educate & refer to dietitian | Follow-up on dietary adherence |
| **Ankle Edema** | Due to fluid retention & NSAIDs | Avoid NSAIDs, use alternative analgesic | Assess swelling reduction |
| **Noncompliance (Medication)** | Forgetting/refusing medications | Medication reminders, pill count | Check refill history & drug adherence |
| **Fatigue/Depression** | Psychological distress | Psychotherapy, consider SSRIs | Assess mood improvement |
| **Smoking** | Heavy smoker | Cognitive Behavioral Therapy (CBT) for smoking cessation | Evaluate smoking reduction |

# 5. Assignment Task

- **Task:** Select a case from **4th or 5th-year clerkship** where **Pharmaceutical Care Plan (PCP)** is needed.
- **Format:** Develop a plan using the **SOAP (Subjective, Objective, Assessment, Plan) format**.
- **Submission:** Take a **snapshot** and send it for review.

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# 6. Self-Revision

- Review **Asthma & Heart Failure Management** strategies.
- Understand the **SOAP format for case documentation**.
- Study **patient adherence improvement techniques**.

# Poison

**Clinical Toxicology - Chapter 7**

Poison can be defined as any substance that causes a harmful effect if administered, by accident or design, to a living organism.

**Quantitative Concept**

- Therapeutic dose
- Long-term chronic toxicity
- Lethality

**Qualitative Concept**

- Species
- Combinations

## Toxin vs. Toxicant

- **Toxin**: Naturally occurring poison (e.g., from plants, animals, or bacteria).
- **Toxicant**: Synthetic or human-made poison.

## Toxicology

Toxicology is a branch of science that deals with poisons. It also includes the study of harmful effects caused by physical phenomena, such as radiation of various kinds and noise.

**Broad Definition**

The study of the detection, occurrence, properties, effects, and regulation of toxic substances.

## Toxicity: A Cascade of Events

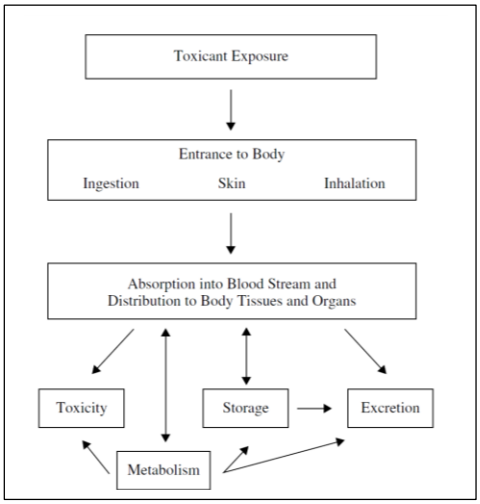
1. **Exposure** (Starting point)
2. **Distribution and Metabolism** (Processing within the body)
3. **Interaction with Cellular Macromolecules** (Usually DNA or protein)
4. **Toxic End Point** (Final harmful effect)

## Types of Toxicity

- **Acute / Chronic** (Short-term vs. long-term toxicity)
- **Organ-Specific / General** (Affecting a single organ or the whole body)

## Factors Affecting Toxicity

- **Age** → Young or old
- **Genetics** → Inherited traits
- **Gender** → Male or female




- **Diet** → Food intake
- **Physiological Condition** → Body function
- **Health Status** → Overall well-being

## Toxicity Measurement

- **LD50** (Lethal Dose 50 – the dose at which 50% of the test dies)
- **Tenfold Variations** (Different routes of exposure can lead varied toxicity levels)

## Branches of Toxicology

1. **Biochemical & Molecular Toxicology** – Study of toxins at the cellular and molecular levels.
2. **Behavioral Toxicology** – Effects of toxins on behavior and the nervous system.
3. **Analytical Toxicology** – Detection and measurement of toxic substances.
4. **Toxicologic Pathology** – Study of tissue and organ damage due to toxins.
5. **Clinical Toxicology** – Diagnosis and treatment of poisoning in humans.
6. **Veterinary Toxicology** – Effects of toxins on animals.
7. **Forensic Toxicology** – Investigation of toxins in legal cases.
8. **Environmental Toxicology** – Study of toxins in the environment and their effects on ecosystems.

## Toxicology Specialties

1. Mechanistic Toxicology
2. Descriptive Toxicology
3. Regulatory Toxicology

## Mechanistic Toxicology

- Focuses on **identifying and understanding** how chemicals cause toxic effects at the **cellular, biochemical, and molecular** levels.
- Used in **risk assessment** (e.g., evaluating **carcinogenicity** and **teratogenicity**).
- Helps determine **adverse reaction relevancy**, like the case of **saccharin**.
- Mechanistic data aids in designing **safer alternatives**, e.g., **Thalidomide** in treating **HIV and leprosy**.
- **STEPS (System for Thalidomide Education and Prescribing Safety)** ensures safe usage.
- Contributes to the understanding of **physiology, biochemistry, and toxicological mechanisms**.

## Descriptive Toxicology

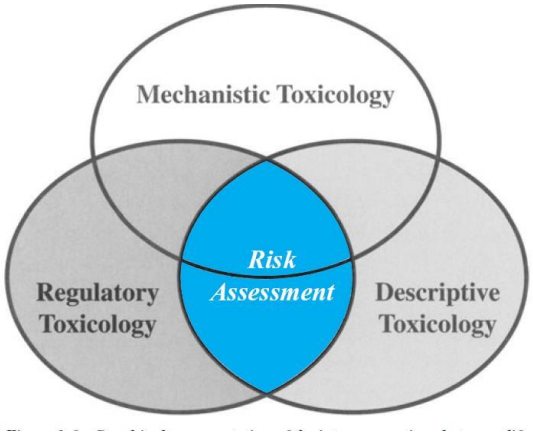
- **Focus**: Direct **toxicity testing** of chemicals.
- **Purpose**: Assesses the **risk posed by toxicants** to **humans, animals, birds, and plants**.
- **Methods**: Uses advanced **"omics" technologies**, including:

- **Genomics** (study of genes)
- **Transcriptomics** (study of RNA)
- **Proteomics** (study of proteins)
- **Metabonomics** (study of metabolic changes)

## Regulatory Toxicology

- **Focus**: Establishing and enforcing **safety regulations** for chemicals and drugs.
- **Key Regulatory Bodies**:
  - **DRAP** (Drug Regulatory Authority of Pakistan)
  - **EPA** (Environmental Protection Agency)
  - **FDA** (Food and Drug Administration)
- **Related Field**: **Forensic Toxicology** – Deals with legal aspects of toxicology, such as poisoning cases and drug regulations.

## Interconnections between different areas of toxicology:




## Classification of Toxic Agents

1. **Source** – **Toxin/Toxicant** (Natural or synthetic substances causing toxicity).
2. **Target Organ** – **Hepatotoxic (Liver)**, **Nephrotoxic (Kidney)**, etc.
3. **Use** – **Pesticides, Insecticides, Rodenticides**, etc.
4. **Chemical Structure** – **Aromatic amines, Halogenated hydrocarbons**, etc.
5. **Poisoning Potential** – **Extremely toxic, Very toxic, Slightly toxic**.
6. **Mechanism of Action** – **Cholinesterase inhibitors, Methemoglobin producers**, etc.
7. **Duration** – **Acute poisons (short-term)** vs. **Chronic poisons (long-term exposure)**.
8. **Environmental Toxins** – Present in **Air, Water, Soil**.

## Spectrum of Undesired Effects

1. **Allergic Reaction** – Immune-mediated response to a substance.
2. **Idiosyncratic Reaction** – Unpredictable and unusual response, not related to dose.
3. **Immediate vs. Delayed Toxicity** – Effects occurring **soon after exposure** vs. **long after exposure**.
4. **Reversible vs. Irreversible Toxic Effects** –
   - **Reversible**: Body recovers after removal of the toxicant.
   - **Irreversible**: Permanent damage (e.g., nerve or organ failure).

5. **Local vs. Systemic Toxicity** –
    - **Local**: Limited to the exposure site (e.g., skin burns).
    - **Systemic**: Affects the whole body or specific organs.
6. **Tolerance** – The body's reduced response to repeated exposure.

## Mechanism of Toxicity

### 1. Acute Toxicity Mechanisms

- **Narcosis** – Suppression of central nervous system activity.
- **Ion Channel Modulators** – Disrupt normal ion flow, affecting nerve and muscle function.
- **Inhibitors of Cellular Respiration** – Block energy production in cells, leading to cell death.
- **Acetylcholinesterase Inhibition** – Prevents the breakdown of acetylcholine, causing overstimulation of nerves.

### 2. Chronic Toxicity Mechanisms

- **Carcinogenesis** – Induction of cancer due to long-term exposure.
- **Teratogenesis** – Toxic effects on fetal development, leading to birth defects.
- **Mutagenesis** – Genetic mutations caused by toxicants.
- **Organ-Specific Toxicity** – Long-term damage to organs like the liver, kidneys, or lungs.

# Drug Information Centers (DIC)

**Definition**

- Operational units that provide **technical and scientific drug information** in an **objective and timely** manner.
- Equipped with **databases, sources of drug information, and trained professionals** to generate independent and relevant drug-related information.
- **First DIC established in 1960 (UK).**

**Requirements for DIC**

- **Personnel:**
  - Director (Pharmacist)
  - Staff pharmacist
  - Internees
- **Facilities & Equipment:**
  - **Physical separate place** for operation
  - Computers
  - Fax/telephone
  - Internet access
  - Books and journals

**Aims and Objectives**

- **Ensure high-quality patient care.**
- **Promote**:
  - Safe, effective, and economic use of medicines.
  - Accurate, timely, appropriate, evidence-based, and unbiased drug information.

**Activities of DIC Services**

Divided into **two main groups**:

1. **Reactive Services:**
   - **Responding to inquiries** regarding:
     - **Prescribing** of medicines.
     - **Supply** of drugs.
     - **Formulation** details.
     - **Administration** of medicines.
   - Mostly focused on **patient-related issues**.

| Enquiry type | Includes |
|---|---|
| **Administration** | Route and timing, techniques and equipment |
| **Adverse effects** | To all medicines, including OTCs and alternative therapies and in all clinical situations (e.g. pregnancy) but excluding poisoning |
| **Alternative therapies** | Homeopathic, herbal, aromatherapy and ethnic therapies |

| Enquiry type | Includes |
|---|---|
| **Availability** | In the UK or abroad for foreign travel |
| **Clinical choice** | Best treatment choice, including most appropriate drug in a therapeutic class, for a specified patient or policy |
| **Indications/contraindications** | For what, and in what situations, a drug can be, or should be, used |
| **Dosage** | Including in children and in specialist clinical situations, e.g. with renal and kidney disease |
| **Drug abuse** | Often in conjunction with drug abuse specialists |
| **Identification** | Generic, OTC, herbal, homeopathic, veterinary and foreign medicines |
| **Incompatibilities** | Normally in intravenous formulations |
| **Interactions** | With other drugs, including OTCs, food and laboratory tests |
| **Pharmaceutics** | Formulation, excipients, stability and analysis |
| **Pharmacoeconomics** | Including cost-effectiveness |
| **Pharmacology/pharmacokinetics** | Mechanism of action and adverse effects and factors associated with metabolism, distribution and excretion |
| **Poisoning/overdose** | Normally referred to the Poisons Information Service |
| **Use in specific situations** | Pregnancy, breast-feeding, with liver or renal disease, with porphyria |

2. **Proactive Services:**

- **Involves producing various informational outputs** to support healthcare professionals and patients.
- **Key Activities Include:**
    - **Bulletins and Newsletters** – Regular updates on drug-related information.
    - **Standardized, Evidence-Based Answers** – Responses to common drug-related questions.
    - **Current Awareness Publications** – Keeping professionals updated on new developments.
    - **Information on New Medicines** – Providing details on newly approved drugs.
    - **Cost Calculator** – Estimating and comparing drug costs for economic use.

## Drug Information Center (DIC) Pharmacist Skills Requirements

1. **Clinical Skills** – In-depth knowledge of pharmacology, therapeutics, and patient care.
2. **Communication Skills** – Ability to effectively convey drug-related information to healthcare professionals and patients.
3. **Information Technology Skills** – Proficiency in using databases, drug information software, and electronic resources.
4. **Training Skills** – Capability to educate healthcare professionals and interns on drug-related topics.

# Chapter 7 | Poison Control Centers (PCC)

## Poison Control Centers (PCC)

- A poisons center is a specialized unit that provides advice on and assists with the **prevention, diagnosis, and management** of poisoning.
- Poisoning can occur by **any route** and due to **various causes**, including **accidental, intentional, occupational, or environmental** exposure.
- The **structure and functions** of poison control centers **vary by country**.
- The **primary role** of a poison control center is to provide **poison-related information**.
- Some centers may also have a **toxicology laboratory** and/or a **clinical treatment unit** for direct patient care.

## Poison Control Centers (PCC) - History and Development

- **First poison control centers** were established in **North America and Europe** during the **1950s**.
- Early poison information centers emerged in various fields, including:
    - **Pediatrics**
    - **Intensive care**
    - **Forensic medicine**
    - **Occupational health**
    - **Pharmacy**
    - **Pharmacology**
- **Veterinary poison centers** exist in **Australia, France, and the USA**.

## Establishment of Poison Control Centers (PCC)

1. **National PCC Satellites** – Network of poison control centers operating at a national level with regional branches.
2. **Location** – Strategically placed in hospitals, research institutions, or emergency medical facilities.
3. **Staff** – Includes toxicologists, pharmacists, physicians, and trained support personnel.
4. **Finances** – Funded through government support, healthcare organizations, and private partnerships.

## Poison Control Centers (PCC) Staff

- **Composition:** Physicians, nurses, chemists, pharmacists, or a combination of these professionals.
- **Variability:** Staff composition depends on local circumstances and resources.
- **Training:** Poisons information staff undergo specialized training in toxicology.
- **Expertise:** Well-equipped with toxicology knowledge.
- **Education:** Often hold postgraduate degrees (PGDs) or specialized courses in toxicology.

## Poison Control Centers (PCC) Functions

1. **Assessment of Exposure** – Evaluating exposure to chemicals, pharmaceuticals, and pesticides.
2. **Hazard Determination & Treatment** – Analyzing toxicity levels and providing treatment options.
3. **Cost-Effective Management** – Ensuring efficient and economical poisoning management.
4. **Database Maintenance** – Keeping records of toxic substances and case reports.
5. **Chemical Incident Preparedness & Response** – Developing protocols for handling chemical emergencies.
6. **Training and Teaching** – Educating healthcare professionals on poison management.

6. **Pharmacovigilance** – Monitoring and reporting adverse drug reactions and toxic effects.
7. **Substance Abuse Management** – Providing information and assistance for drug and alcohol poisoning cases.
8. **Environmental Toxicology** – Assessing and managing toxic environmental exposures.

## Process of Poison Control Centers (PCC)

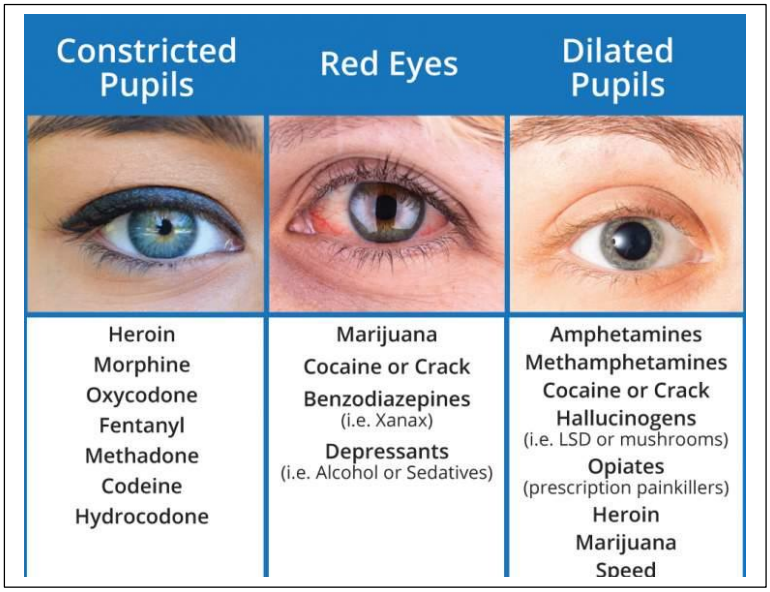
1. **Access** – 24/7 availability via telephone, email, or written requests; face-to-face consultations.
2. **Inform** – Providing information on diagnosis, prevention, prognosis, and treatment.
3. **Lab** – Conducting investigations using instruments, hematology, biochemistry, assays, and HPLC.
4. **Manage** – Utilizing own facilities or referring cases; providing first aid treatment.

# Management of Poisoning

**Toxicological Investigations:** Routine investigations valuable in poison-induced conditions include:

- **Electrolyte Imbalances**
  - Hypokalaemia
  - Hyperkalaemia
- **Glucose Levels**
  - Hypoglycaemia
  - Hyperglycaemia
- **Organ Failures & Disturbances**
  - Hepatic or renal failure
  - Acid-base disturbances
- **Specific Measurements**
  - Carboxyhaemoglobin
  - Methaemoglobin

**General management of poisoning:**




## Supportive Management

### 1. Respiratory Support:

- Respiratory depression
- Loss of cough or gag reflex → Oropharyngeal airway & oxygen therapy
- Ventilator support

### 2. Cardiovascular Support:

- Hypotension
- Cardiovascular shock
- Correction of arrhythmogenic factors:
  - Hypoxia
  - Acidosis
  - Hypokalemia

## Temperature Management in Poisoning

### Hypothermia (Below 35°C):

- Recognized complication of poisoning
- Covered with a *space blanket*
- Use intravenous and intragastric fluids at normal body temperature
- Inspired gases should be warmed to 37°C

### Hyperthermia:

- Remove clothing
- Sponge with water to promote evaporation

## Specific Management of Poisoning

1. **Antidotes**
2. **Reduction of Poison Absorption**
    - Inhaled
    - Skin
    - Gut
3. **Increasing Poison Elimination**
    - Gastric Lavage
    - Cathartics
    - Ipecac

# Benzodiazepine (BZD) Toxicity

### Overview

- Isolated BZD toxicity is rare.
- Serious toxicity occurs when combined with alcohol and opioids.
- In 2018, the US poison control centers reported **22,995** cases.
    - **469 (2%)** resulted in major toxicity.
    - **19 cases** resulted in death.
- Cases involving BZDs with alcohol or other drugs show significantly higher numbers.

### Presentation of Acute Poisoning

1. **Mild Symptoms**
    - Drowsiness
    - Ataxia
    - Weakness
2. **Moderate to Severe Symptoms**
    - Vertigo
    - Slurred speech
    - Nystagmus
    - Partial ptosis
    - Lethargy
    - Coma
    - Hypotension
    - Respiratory depression

### History Assessment

- Time of ingestion
- Dose taken / Co-ingestants (if any)
- Whether overdose was accidental or intentional
- Duration of BZD use

## Physical Examination in Benzodiazepine Toxicity

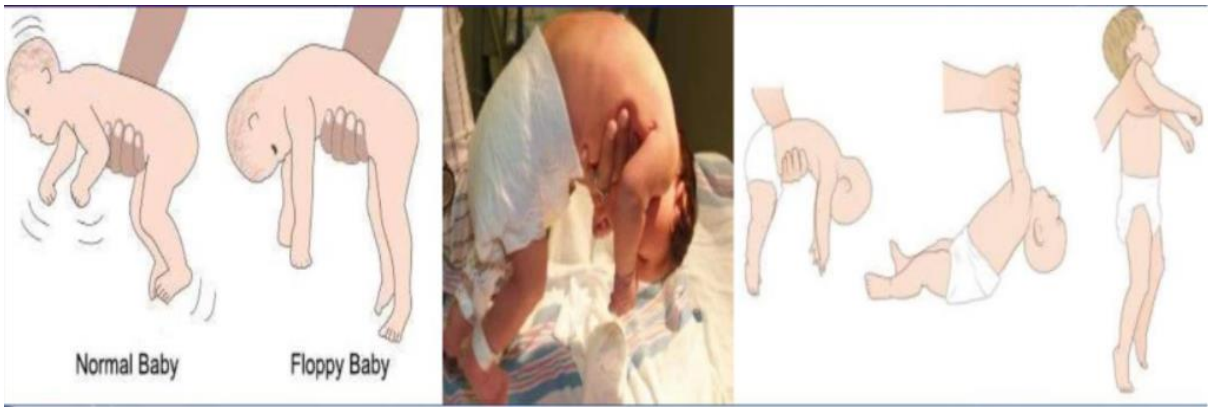
### Classic Presentation

- **"Classic" isolated benzodiazepine overdose** presents as **coma** with **normal vital signs**.

**Physical Examination Findings**

- **Nystagmus**
- **Hallucinations**
- **Slurred speech**
- **Ataxia**
- **Coma**
- **Hypotonia** (reduced muscle tone)
- **Weakness**
- **Altered mental status** and **cognitive impairment**
- **Amnesia**
- **Paradoxical agitation** (opposite of sedation, leading to restlessness or aggression)
- **Respiratory depression**
- **Hypotension**

## Pregnancy:




## Diagnosis of Benzodiazepine Toxicity

1. **Qualitative Testing**
    - Used to confirm the presence of benzodiazepines in the body.
2. **Quantitative Levels**
    - Measures the concentration of benzodiazepines in blood or urine to assess severity.
3. **Skin Manifestations**
    - **Blisters (bullae)** may occur following an overdose with:
        - **Nitrazepam**
        - **Oxazepam**
        - **Temazepam**

## Diagnostic Tests for Benzodiazepine Toxicity

- **Tests and procedures depend on the presentation:**
    1. **ABG assay** (if respiratory depression is present)
    2. **ECG** (to evaluate for co-ingestants, particularly cyclic antidepressants)

3. **Chest radiograph** (if respiratory compromise is present)
4. **Pregnancy test** (in women of childbearing age)

- **In cases of intentional overdose, measure the following:**
  1. **Serum electrolytes**
  2. **Glucose**
  3. **BUN (Blood Urea Nitrogen)**
  4. **Creatinine clearance**
  5. **Ethanol level**

---

## General Management of Benzodiazepine Toxicity

1. **Monitor**
   - CBC, serum electrolytes, glucose, BUN, creatinine, and urine myoglobin (in cases of significant intoxication).
2. **Gastric Lavage**
   - Preferably done using a large-bore, double-lumen tube.
   - Can be beneficial up to **12 to 24 hours post-ingestion**.
3. **Multiple Dose Activated Charcoal**
   - Shown to be effective in absorbing benzodiazepines.
4. **Airway Management**
   - Establish a **clear airway**.
   - **Oxygen and assisted ventilation** may be necessary.
5. **IV Fluids**
   - **Ringer's lactate** at **150 ml/hr** for adults.
6. **Correction of Hypotension**
   - Begin with **10 to 20 ml/kg of isotonic fluid**.
   - Place patient in **Trendelenburg position**.
   - If hypotension persists, administer **dopamine or noradrenaline**.
   - Consider **central venous pressure (CVP) monitoring** for fluid therapy guidance.

---

## Flumazenil Therapy (Benzodiazepine Antidote)

- **Flumazenil reverses benzodiazepine-induced coma.**
- Most patients achieve **complete reversal** with a **total slow IV dose of 1 mg**.
- It is better administered in **incremental doses**, starting with **0.2 mg**, increasing **by 0.1–0.2 mg per minute** until a cumulative **3.5 mg dose is reached**.
- **Resedation occurs within 30 minutes to 2 hours**, depending on the dose and type of benzodiazepine.
- **Continuous Flumazenil infusion (5–24 hours)** may be needed in cases of resedation.
- **Flumazenil reverses cardiovascular depression** ✓
- **Flumazenil does not effectively reverse respiratory depression** ✗
- **Flumazenil is contraindicated in mixed drug ingestions** (e.g., co-ingestion with TCAs, opioids, or other CNS depressants) ⚠

## Case Report: Alprazolam Overdose

**Patient Details:**

- **Age:** 37 years
- **History:** Psychiatric problems, panic disorder

**Presentation:**

- **Unconscious state**
- **Alleged ingestion:** 60 tablets of Alprazolam (3 hours prior)
- **Intent:** Suicide attempt
- **Medication History:** Alprazolam and Fluoxetine

**Physical Examination:**

- **Deep coma**
- **Bilateral constricted pupils (minimal reaction to light)**
- **Diminished tendon reflexes**
- **Urine retention**
- **Plantar reflexes absent bilaterally**
- **No response to painful stimuli**

**Vital Signs on Admission:**

- **Pulse:** 100/min (feeble)
- **Blood Pressure:** 80 mmHg (systolic)
- **Respiratory Rate:** 30/min (regular)
- **Temperature:** 36.8°C

---

## Management

- **Diagnosis:** Alprazolam overdose
- **Interventions:**
    1. **Nasogastric tube placement** and **catheterization**
    2. **Gastric lavage** (no pill fragments recovered)
    3. **Urgent intubation** and **mechanical ventilation** with continuous oxygen
    4. **Parenteral fluids** administered
    5. **Flumazenil** (benzodiazepine antidote) given

**Outcome:**

- **Patient showed improvement after a few hours**
- **Extubated successfully**
- **Recovered and discharged**

# Compliance & Non-Compliance in Healthcare

### Definition of Compliance

The **World Health Organization (WHO)** defines compliance as a patient's ability to follow health-related behaviors, including:

- Taking prescribed medications correctly.
- Adopting a healthy lifestyle.
- Following the recommendations of healthcare professionals.

---

## Non-Compliance: The "Invisible Epidemic"

- **Non-compliance** occurs when patients do not follow medical advice, leading to ineffective treatment.
- It is often **unnoticed** but has significant consequences on health outcomes.

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## The Five Dimensions of Adherence

| Dimension | Explanation | Examples |
|---|---|---|
| **1. Social & Economic** | External factors affecting a patient's ability to follow treatment. | Low income, lack of social support, high medication costs. |
| **2. Health Care System** | The role of healthcare providers and system accessibility. | Poor communication with doctors, long wait times, lack of insurance. |
| **3. Condition-Related** | Factors linked to the patient's illness. | Chronic conditions needing lifelong treatment, asymptomatic diseases (e.g., high blood pressure). |
| **4. Therapy-Related** | Issues related to the treatment itself. | Complex medication regimens, side effects, long treatment duration. |
| **5. Patient-Related** | Personal behaviors, beliefs, and understanding of treatment. | Forgetfulness, fear of side effects, lack of motivation. |

## Detection of Non-Compliance

| Method | Examples |
|---|---|
| **Direct Methods** | Biomarker testing, Measuring drug levels in blood |
| **Indirect Methods** | Patient interviews, Counting remaining pills, Evaluating treatment effectiveness, Monitoring via electronic medication systems (MEMS) |

# Factors Responsible for Non-Compliance

| Category | Factors |
|---|---|
| **1. Disease-Related Factors** | Psychiatric disorders, Hypertension, High cholesterol (Hypercholesterolemia), Rheumatoid arthritis |
| **2. Treatment-Related Factors** | Multiple medications, Frequent dosing, Long treatment duration |
| **3. Dosage Form Issues** | **Liquid medications** – Taste issues; **IV (Intravenous)** – Requires expertise, painful; **Suppositories** – Social discomfort; **Tablets** – Large size, difficult to swallow |
| **4. Treatment Duration** | Lifelong therapies (e.g., diabetes, hypertension), Long antibiotic courses |
| **5. Side Effects** | Fear of adverse effects, Drowsiness (CNS effects), Sexual dysfunction, Hangover-like symptoms |
| **6. Cost of Therapy** | Expensive medications, Limited access to affordable brands |
| **7. Patient-Provider Interaction** | Complex medical terms, Lack of communication time |

# Consequences of Non-Compliance

| Outcome | Effect |
|---|---|
| **Underuse of Medication** | Disease worsens due to insufficient treatment |
| **Overuse of Medication** | Risk of toxicity and overdose |
| **Adverse Drug Reactions (ADRs)** | Unexpected side effects from improper use |
| **Drug Resistance** | Ineffective treatment due to misuse of antibiotics |
| **Waste of Resources** | Increased healthcare costs and wasted medications |
| **Hospitalization** | Severe health deterioration leading to hospital admission |
| **Drug Abuse** | Misuse of prescribed drugs for non-medical reasons |

# Improving Compliance

## 1. Identifying Risk Factors

- Recognizing **patients at risk** of non-compliance and addressing their concerns.

## 2. Patient Education

| Method | Purpose |
|---|---|
| **Oral Communication** | Direct patient counseling |
| **Written Instructions** | Easy-to-follow medication guides |
| **Audiovisual Aids** | Videos or demonstrations to explain proper medication use |
| **Patient Motivation** | Encouraging adherence through reminders and support |

### 3. Compliance Aids

| Tool | Function |
|---|---|
| **Proper Labeling** | Clear instructions on medication packaging |
| **Compliance Containers** | Pill organizers to manage doses |
| **Modified Dosage Forms** | Extended-release (SR) tablets for less frequent dosing |

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# Theories of Health Behavior

Health behavior theories explain why people make health-related choices and how they can be influenced to adopt healthier behaviors. These models help in designing effective health interventions.

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## 1. Behavioral Model

This model focuses on how personal characteristics, lifestyle, and external influences shape health behaviors.

| Key Concepts | Explanation |
|---|---|
| **Personality & Lifestyle** | Individual traits and daily habits impact health. |
| **Responsibility for Health** | People take charge of their own health choices. |
| **Stimulus Response** | Behaviors can be conditioned through external triggers. |
| **Incentives & Reminders** | Rewards and reminders help reinforce health behaviors. |
| **Learning by Observation** | Watching, listening, and reading can improve behaviors. |

### Rotter's Locus of Control

Describes how much control individuals believe they have over their health.

| Locus of Control | Belief System | Impact on Health |
|---|---|---|
| **Internal** | "I control my health through my actions." | More likely to follow medical advice and adopt healthy behaviors. |
| **External** | "My health is controlled by external factors (e.g., luck, doctors, environment)." | Less proactive in taking health measures. |

💡 **Internal locus is linked to better health compliance and quality of life.**

---

## 2. Health Belief Model

This model explains how personal beliefs influence health behavior.

| Key Components | Explanation |
|---|---|
| **Perceived Susceptibility** | Belief about the likelihood of getting a disease. |
| **Perceived Severity** | Understanding how serious the disease and its consequences are. |
| **Perceived Benefits** | Belief that taking action will have positive effects. |
| **Perceived Barriers** | Recognizing and overcoming obstacles to action. |

💡 **Example:** A person at risk for diabetes may adopt a healthier lifestyle if they believe they are susceptible and see benefits in prevention.

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## 3. Self-Efficacy

Self-efficacy refers to the belief in one's ability to succeed in health-related tasks.

💡 **Example:** A Type 2 diabetic patient believes they can manage their condition through exercise, diet, and stress management.

---

## 4. Protection Motivation Theory

People make health decisions based on their perception of threats.

| Key Idea | Impact on Behavior |
|---|---|
| If a person perceives a serious health threat | They are more likely to take preventive action. |

💡 **Example:** A smoker who understands the risk of lung cancer is more likely to quit smoking.

---

## 5. Self-Medication Hypothesis

People make independent decisions about their medication.

| Key Aspects | Explanation |
|---|---|
| **Self-adjustment** | Patients may start, stop, or change medication based on how they feel. |

| Key Aspects | Explanation |
|---|---|
| **Perceived Health Needs** | Decisions are often based on personal judgment rather than medical advice. |

💡 **Example:** A person with a headache may decide to take painkillers without consulting a doctor.

---

# 6. Biomedical Model

This model focuses on biological factors and medical treatment.

| Key Aspects | Explanation |
|---|---|
| **Disease Characteristics** | The nature and severity of an illness affect health decisions. |
| **Fear of Side Effects (ADRs)** | Concerns about adverse drug reactions impact medication adherence. |
| **Role of Medical Professionals** | Doctors provide essential support and treatment. |
| **Simplified Treatment** | Clear dosing instructions and easy packaging improve adherence. |

---

# 7. Educational Model

This model highlights the role of education in health behavior.

| Key Components | Explanation |
|---|---|
| **A. Communication** | Informing patients with trust and empathy. |
| **B. Self-Regulation** | Patients actively manage their own health. |

### Components of Self-Regulation

1. **Standards** – Setting personal health goals.
2. **Motivation** – Staying committed to health improvements.
3. **Monitoring** – Tracking progress.
4. **Willpower** – Maintaining discipline to achieve goals.

💡 **Example:** A person trying to lose weight tracks their diet and adjusts based on results.

---

# 8. Transtheoretical Model (TTM) – Stages of Change

The **Transtheoretical Model (TTM)** explains how individuals change behavior over time through different stages. It is often used for health behaviors like quitting smoking.

| Stage | Description | Example (Smoking Cessation) |
|---|---|---|
| **Precontemplation** | No intention to change behavior within the next 6 months. | A smoker who is not considering quitting. |
| **Contemplation** | Thinking about change but not ready yet (within the next 6 months). | A smoker who is considering quitting but has not set a specific date. |
| **Preparation** | Actively planning to change within the next 30 days and has made an attempt before. | A smoker who plans to quit soon and has already tried quitting for 24 hours in the past year. |
| **Action** | Recently changed behavior (within the last 6 months). | A person who has quit smoking but has not yet reached long-term stability. |
| **Maintenance** | Sustaining the new behavior for more than 6 months. | A former smoker who has not smoked for over 6 months and is working to prevent relapse. |

# Safe Intravenous (IV) Therapy & Hazards

## Intravenous Therapy (IV Therapy)

Intravenous therapy involves the infusion of solutions, medications, blood, or blood products directly into a vein. It is widely used in hospitalized patients (80%) due to its effectiveness, speed, and necessity in emergencies or for comatose patients.

### Types of IV Therapy

| Type | Description |
|---|---|
| **Peripheral IV Therapy (PIVT)** | Used for short-term treatment in small veins. |
| **Central IV Therapy (CIVT)** | Long-term treatment via the superior vena cava. |

### IV Solutions

| Type | Description |
|---|---|
| **Colloid Solutions** | Contain large molecules (e.g., Albumin, Dextran). |
| **Crystalloid Solutions** | Contain electrolytes and dextrose. |
| **Based on Tonicity** | Includes isotonic, hypertonic, and hypotonic solutions. |

### Common Reasons for IV Therapy

1. Fluid and electrolyte replenishment
2. Antibiotic administration (40% of all IV treatments)
3. Blood transfusion
4. Parenteral nutrition

## Guidelines for Safe IV Therapy

### 1. Maintaining Hygiene

- Aseptic technique and proper hand hygiene.
- Proper preparation and maintenance of equipment.
- Prompt replacement if contamination occurs.

### 2. Accurate Information

- Physician’s order must include:
    - Type of drug
    - Infusion rate
    - Duration and timing

## 3. Setting Up a Peripheral IV Line

- Upper extremity veins preferred.
- Use percutaneous vein puncture.
- Apply sterile transparent dressing to prevent dislodgement.
- Use positive pressure cap in catheter hub.

## 4. Discontinuation of Peripheral IV Line

- IV line should be changed every **72-96 hours**.
- Removed if patient is stable or showing signs of complications (tenderness, swelling, redness, drainage).
- Change administration set (IV tubing) accordingly.

## 5. Central Venous Catheters (CVCs)

- Also known as a **central line**, inserted into the superior vena cava.
- Inserted surgically by trained personnel using ultrasound or X-ray.
- Used for patients requiring long-term IV therapy (>6 days) and can be retained for up to **1 year**.

**Indications for CVC Use:**

- Antineoplastic medications
- Serious or chronic illnesses
- Irritant/toxic medications
- Need for central venous pressure monitoring
- Long-term venous access (e.g., dialysis, total parenteral nutrition)
- Medications with extreme pH values (>9 or <5) or high osmolality (>600 mOsm/L)
- Poor venous access or multiple failed PIV attempts

## 6. IV System Assessment

- Must be checked every **1-2 hours** and at the beginning and end of shifts.
- Look for **pain, tenderness, swelling, or discomfort** at the insertion site.
- Replace PIV every **72 hours**.
- Flush non-in-use PIV sites every **12 hours**.

## 7. Types of IV Solutions

| Type | Examples |
|---|---|
| **Colloid Solutions** | Albumin, Dextran |
| **Crystalloid Solutions** | Electrolytes, Dextrose |

# Complications of Intravenous (IV) Therapy: Air Embolism

## Definition

- **Air Embolism**: The presence of gas in the bloodstream, leading to potential complications.
- **Venous Air Embolism (VAE)**: A subset of gas embolism, often subclinical but can be fatal in large volumes.
- **Significance**:
  - **> 5 mL/kg** of air can cause severe injury.
  - **2–3 mL** of air in the cerebral circulation may be fatal.

## Pathophysiology of Air Embolism

| Effects | Consequences |
|---|---|
| **Pulmonary artery pressure increases** | Right ventricular (RV) ejection decreases |
| **Reduced venous return** | Cardiac output (CO) drops → Cardiogenic shock |
| **Pulmonary vasculature effects** | Inflammatory changes, endothelial damage, platelet & fibrin accumulation |
| **Pulmonary complications** | Pulmonary edema, ventilation-perfusion mismatch |

## Causes of Air Embolism

| Cause | Description |
|---|---|
| **Peripheral IV therapy** | Air entering veins due to improper IV handling |
| **Central IV therapy** | Higher risk due to direct access to large veins |
| **Surgical procedures** | Air entry during surgeries involving major veins |

---

**Table 2. Examples of Nonoperative Procedures Associated with Vascular Air Embolism**

- **Direct vascular procedures:**
  - Central venous access related
  - Radial artery catheterization
  - Parenteral nutrition therapy
  - Interventional radiology
- **Pain management procedures:**
  - Epidural catheter placement (loss of resistance to air technique)
- **Diagnostic procedures:**
  - Contrast-enhanced CT
  - Contrast-enhanced CT chest(Comp. Tomography)
  - Lumbar puncture
  - Thoracentesis
- **Hemoperfusion procedures:**
  - Intraaortic balloon rupture
  - Rapid blood cell infusion systems
  - Blood storage container

## Signs and Symptoms

- **Abrupt onset** of symptoms
- **Respiratory Issues**: Sudden dyspnea, cough, wheezing
- **Chest Discomfort**: Chest and/or shoulder pain
- **Cardiovascular Signs**: Tachycardia, hypotension, systolic murmur
- **Neurological Symptoms**: Stroke-like symptoms (cerebrovascular accident)
- **Severe Outcome**: Can lead to death

## Diagnosis of Air Embolism

| Diagnostic Method | Purpose |
|---|---|
| **CT Scan** | Detects air bubbles in circulation |
| **MRI** | Identifies brain involvement in cerebral air embolism |
| **Ultrasound Doppler** | Detects air in the venous system |

## Treatment of Air Embolism

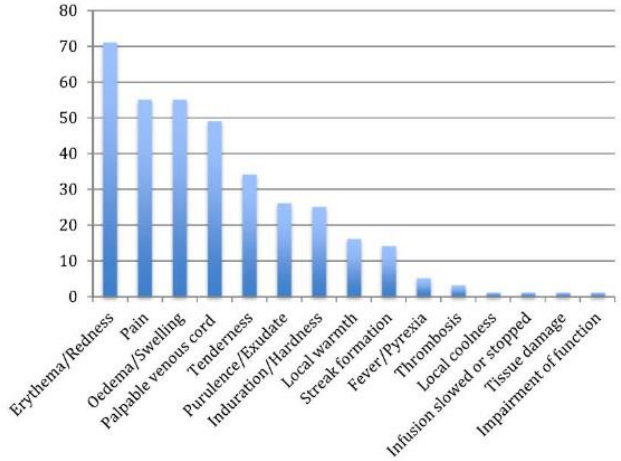
| Treatment Step | Action |
|---|---|
| **Stop Infusion** | Clamp the IV line to prevent further air entry |
| **Oxygen Therapy** | Increase oxygen supply to reduce hypoxia |
| **Intubation** | Endotracheal intubation if needed for respiratory distress |
| **CPR** | If cardiac arrest occurs, initiate resuscitation |
| **Supportive Care** | Vasopressors and mechanical ventilation may be required |

---

# Phlebitis: A Complication of IV Therapy

## Definition

- **Phlebitis**: Inflammation of a vein, commonly affecting peripheral veins.
- **Affects**: **Tunica intima** (inner layer of the vein).
- **Can Lead to**: **Thrombophlebitis** (clot formation with inflammation).
- **Common in**: Individuals aged **40-60 years**.
- **Types**: **Superficial or Deep**.
- **Symptoms**: Pain, redness, swelling.



## Types of Phlebitis and Causes

| Type | Cause | Prevention |
|---|---|---|
| **Mechanical Phlebitis** | Caused by cannula friction or injury to tunica intima | Use small-gauge cannula |
| **Chemical Phlebitis** | Due to strongly alkaline, acidic, or hypertonic drugs in small veins | Proper drug dilution & sufficient blood flow |
| **Infective Phlebitis** | Microorganisms entering through the puncture site due to poor hygiene | Aseptic technique & proper site care |

---

## Visual Infusion Phlebitis Score:

| Score | Criteria | Action |
|---|---|---|
| **0** | IV site appears healthy | No sign of phlebitis, observe cannula |
| **1** | One of the following is evident: • Slight pain near IV site • Slight redness near IV site | Possible sign of phlebitis, observe cannula |
| **2** | Two of the following are evident: • Pale near IV site • Erythema • Swelling | Early stage of phlebitis, resite cannula |
| **3** | All of the following are evident: • Pain along path of cannula • Erythema • Induration | Medium stage of phlebitis, resite cannula, consider treatment |
| **4** | All of the following are evident and extensive: • Pain along path of cannula • Erythema • Induration • Palpable venous cord | Advanced stage of phlebitis or start of thrombophlebitis, resite cannula, consider treatment |
| **5** | All of the following are evident and extensive: • Pain along path of cannula • Erythema • Induration • Palpable venous cord • Pyrexia | Advanced stage of thrombophlebitis, initiate treatment, resite cannula |

---

# Management of Phlebitis

- **Remove the cannula** if the **VIP score is 2 or greater** to prevent further complications.
- **Dilute irritating solutions** before administration to reduce vein irritation.
- **Decrease the speed of infusion** to minimize mechanical stress on the vein.
- **Reinsert a new small-gauge cannula** if clinically necessary, ensuring minimal trauma.
- **Place the cannula away from points of flexion** to reduce movement-related irritation.
- **If the VIP score reaches 5**, take a **swab for culture** to assess for infection.

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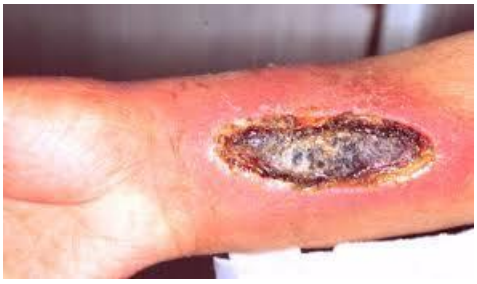
# Extravasation



- **Definition**: The leakage of vesicant drugs into surrounding tissues, leading to severe local tissue damage.
- **Incidence**: Occurs in **0.5% to 6%** of patients receiving chemotherapy.
- **High-Risk Patients**:
  - Cancer patients due to multiple infusions.
  - Patients with **malnourishment** (weakened tissues).
  - Those experiencing **side effects of chemotherapy and radiotherapy** (compromised veins and skin integrity).

## Chemotherapeutic agents listed according to local toxicity:

| Category | Agents |
|---|---|
| **Vesicant** | Doxorubicin, epirubicin, daunorubicin, idarubicin, dactinomycin (anthracyclines) Vincristin, vinblastin, vindesin, vinorelbine, vinflurin (vinca alkaloids) Mitomycin-C, mechlorethamin, carmustin (alkylating agents) |
| **Irritants** | Mitoxantrone, aclarubicin (DNA-intercalating antibiotics) Etoposid, teniposid (epipodo-phyllotoxin) Fluorouracil, floxuridin (antimetabolites) Cisplatin, carboplatin, dacarbazin, oxaliplatin (alkylating or DNA-binding) Paclitaxel, docetaxel, bleomycin (others) |
| **Non-Vesicants** | Metotrexat, cytarabin, pentostatin, gemcitabin, capecitabin (antimetabolites) Cyklofosfamid, ifosfamid, melphalan (alkylating agents) Irinotecan, topotecan, trastuzimab (others) |

Here is the organized and structured text on **IV Therapy and Its Hazards**:

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# Extravasation Pathophysiology

### Steps of Extravasation Pathophysiology

1. **Sites-specific free radical damage**
2. **DNA damage**
3. **Drug-DNA complexes diffuse into adjacent tissue**
4. **Induced tissue necrosis may deteriorate tissue**

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# Extravasation Clinical Signs and Symptoms

### Early Signs:

- Pain
- Irritation
- Swelling
- Erythema
- Blistering

**Late Signs:**

- Induration
- Ulceration
- Long-term pain
- Tissue necrosis
- Joint destruction
- Permanent dysfunction and cosmetic changes

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# Extravasation Management

- Discontinue infusion
- Administer antidote
- Do not flush the cannula
- Attempt to aspirate the drug from the cannula
- Apply topical steroids
- Surgery if necessary

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# Infection in IV Therapy

**Causes of Infection:**

- Cannula insertion
- Poor management and care
- Lack of aseptic techniques
- Local infection (which can sometimes become systemic)

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# Infection Clinical Signs and Symptoms

- Redness
- Swelling and localized induration
- Skin discoloration
- Purulent discharge
- Pain
- Severe systemic infection (e.g., fever)

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# Infection Management

- Take a swab from the insertion site for culture
- Remove the cannula and culture it
- Clean the insertion site with an antimicrobial wipe
- Place a sterile dressing over the site
- Notify medical staff

**Additional Infection Management:**

- Systemic antibiotics may be necessary
- Monitor the site every 8 hours
- Document all actions taken

# Stroke

*Chapter 10, Unit V: Introduction to Neurological Disorders*

## Neurological Disorders

Neurological disorders affect the **brain, spinal cord, and associated tracts**, leading to various functional impairments.

### Categories of Neurological Disorders

| Affected Area | Description |
|---|---|
| **Brain** | Disorders impacting cognition, movement, and consciousness (e.g., stroke, epilepsy). |
| **Spinal Cord** | Conditions affecting motor and sensory functions (e.g., spinal cord injury, multiple sclerosis). |
| **Associated Tracts** | Issues in nerve pathways that transmit signals (e.g., neuropathies, ALS) |

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# Neurological Disorders- Brain Functions Change

| Condition | Definition |
|---|---|
| **Hemorrhage** | Bleeding due to the rupture of a blood vessel in the brain. |
| **Tumor** | Abnormal growth of brain cells, which can be benign (non-cancerous) or malignant (cancerous). |
| **Brain Damage** | Permanent or temporary impairment due to injury, disease, or lack of oxygen. |
| **Infections** | Inflammation caused by bacteria, viruses, fungi, or parasites affecting the brain and spinal cord. |
| **Infarction** | Tissue death due to a lack of blood supply, commonly caused by a stroke. |
| **Hemodynamics** | The study of blood flow and circulation, crucial for brain function. |
| **Brain Function Changes** | Alterations in brain activity due to injury, disease, or external factors. |

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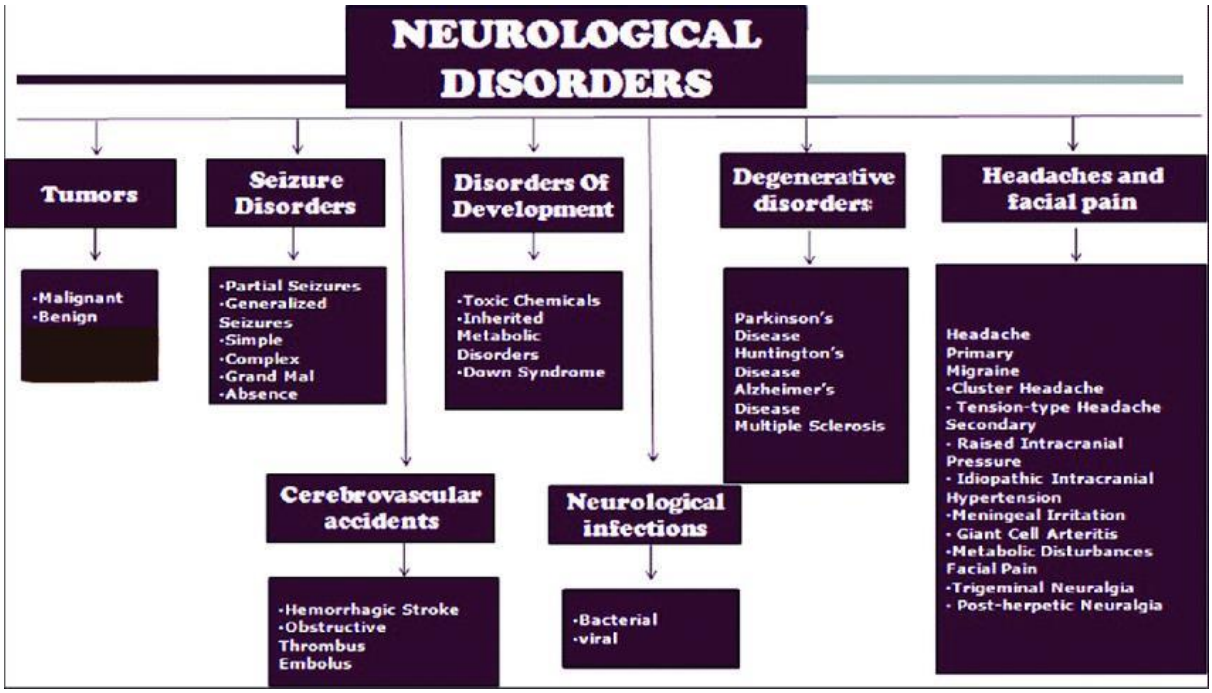
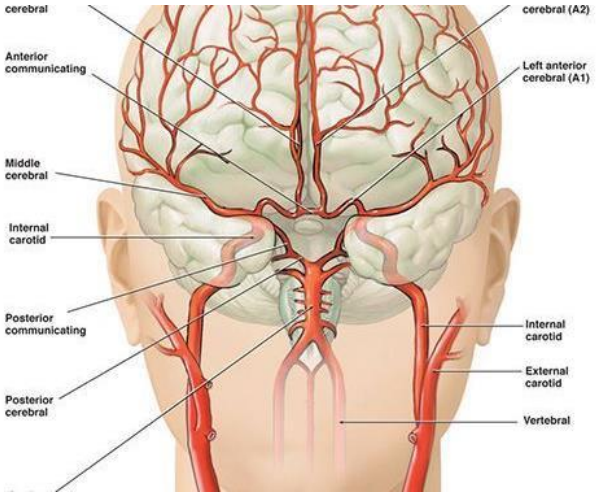



# Cerebral Circulation and Auto-Regulation

## Auto-Regulation

The brain maintains stable blood flow despite changes in blood pressure.




## Concept of Effective Perfusion Pressure

Balance between arterial pressure, venous pressure, and intracranial pressure to ensure adequate blood flow.

## Theories of Auto-Regulation

| Theory | Mechanism |
|---|---|
| **Myogenic** | Response of blood vessels to pressure changes. |
| **Metabolic** | Regulation based on metabolic demand. |
| **Neural** | Autonomic nervous system control. |
| **Cushing Reaction** | Response to increased intracranial pressure. |

## Cerebral Blood Flow (CBF)

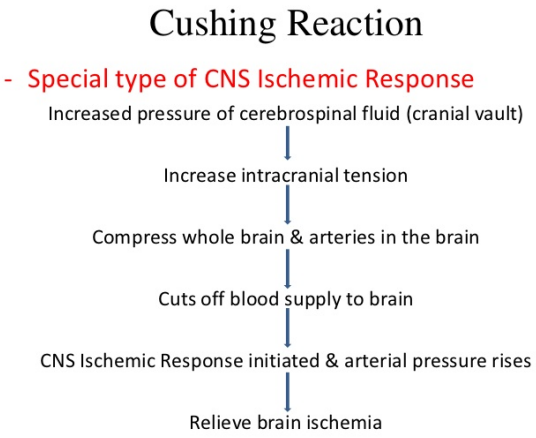
| Parameter | Value |
|---|---|
| **Percentage of Cardiac Output** | 16-20% |
| **Flow Rate** | 1300 ml/min |
| **Perfusion Rate** | 55 ml/100 gm of brain tissue |

## Major Arteries Supplying the Brain

| Artery | Function |
|---|---|
| **Basilar Artery** | Supplies the posterior brain. |
| **Internal Carotid Artery** | Supplies the anterior brain. |

## Circle of Willis

Formed by branches of the basilar and internal carotid arteries, ensuring collateral circulation.

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# Intracranial Hypertension (IIH) & Intracranial Pressure (ICP)

## 1. Intracranial Pressure (ICP)

| | |
|---|---|
| **Definition** | The pressure inside the skull, affecting brain tissue and cerebrospinal fluid (CSF). |
| **Measurement Unit** | mm Hg |
| **Normal Level** | 7-15 mm Hg |

### ICP Maintenance

| Factor | Details |
|---|---|
| **CSF Production & Absorption** | 500 ml produced, 100-150 ml circulates |
| **Brain Mass** | 1.5 kg |
| **Blood Flow** | 16% of cardiac output (CO), 1300 ml/min |

### Monro–Kellie Hypothesis

Describes the pressure-volume relationship between ICP, CSF volume, blood, and brain tissue.
Compensation mechanisms exist to maintain equilibrium.

# 2. Idiopathic Intracranial Hypertension (IIH)

| | |
|---|---|
| **Definition** | Elevation of pressure in the cranium, also known as Pseudotumor Cerebri or Benign Intracranial Hypertension (BIH). |
| **Normal ICP** | 7–15 mm Hg |
| **Upper Limit** | 20–25 mm Hg |

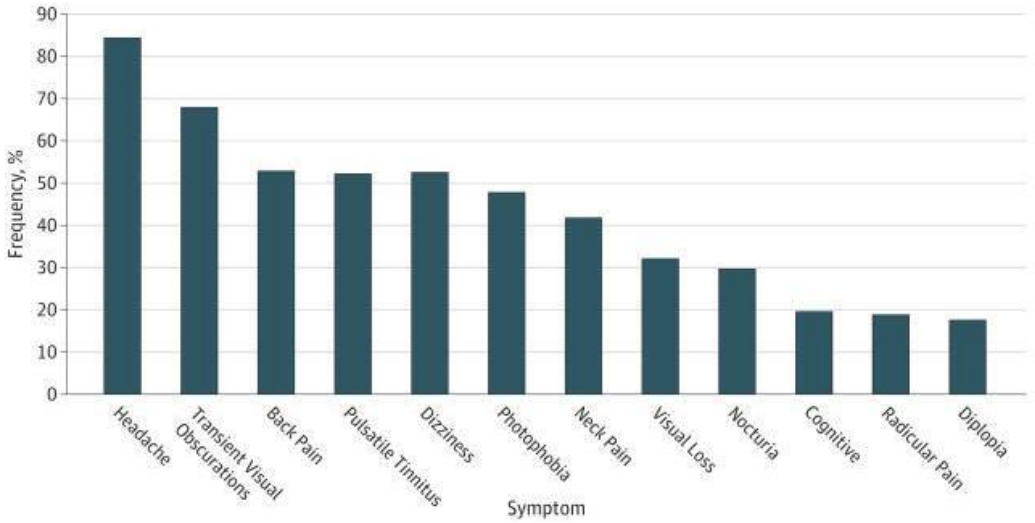
### Pathophysiology of IIH

| Factor | Explanation |
|---|---|
| **Obstruction** | Narrowing of transverse dural venous sinus (MR venography studies). |
| **Increased Blood Flow** | Leads to increased pressure. |
| **Obesity** | Affects venous emptying in SVC due to increased abdominal pressure. |

# 3. Clinical Presentation

| Symptom | Description |
|---|---|
| **Headache** | Persistent and severe. |
| **Papilledema** | Swelling of the optic nerve. |
| **Diplopia** | Double vision. |
| **Vision Issues** | Loss, obscurity. |
| **Nausea & Vomiting** | Common due to pressure changes. |
| **Bradycardia** | Slow heart rate. |
| **Hyperventilation** | Rapid breathing response to increased ICP. |

## Idiopathic intracranial hypertension treatment trial (IIHTT)



## 4. Diagnosis

| Method | Procedure |
|---|---|
| **Physical Exam & History** | Clinical assessment. |
| **Optic Disc Examination** | Fundoscopy. |
| **Imaging** | CT Scan, MRI, MRV. |
| **Blood Tests** | CBC, Cardiolipin antibodies, Coagulation profile. |
| **Lumbar Puncture** | CSF physical, chemical, and culture analysis. |

## 5. Treatment of IIH

### Goals

- Preserve optic nerve function.

| Treatment | Details |
|---|---|
| **Acetazolamide (AZM)** | Improves vision loss, ICP, and headaches (47%-60% success rate). |
| **Headache Management** | Amitriptyline, Propranolol, Topiramate. |
| **Corticosteroids** | Used for severe cases. |
| **Surgical Options** | Optic Nerve Sheath Fenestration, CSF Diversion, Venous Sinus Stenting. |

### IIH Long-Term Study (NIH)

- 165 patients with IIH and mild vision loss.
- 38% recurrence over 6.2 years; no recurrence in those on continuous acetazolamide treatment.

---

# Case History

| Patient Details | Information |
|---|---|
| **Age** | 32 years |
| **Gender** | Female |
| **Marital Status** | Unmarried |
| **Occupation** | Assistant Professor of Gynecology |
| **Medical History** | History of migraine |
| **Medications Used** | Triptans (not relieved) |

## Clinical Course

| Event | Details |
|---|---|
| **Chief Complaint (CC)** | Severe headache for the last 2 days. |
| **Initial Visit** | Presented to LRH Emergency with headache. |
| **Initial Treatment** | Given anti-migraine drugs and sent home. |
| **Condition Worsened** | Experienced a more severe headache attack. |
| **Readmission** | Admitted to Neurology. |
| **Investigations** | MRI and MRV performed. |
| **Diagnosis** | Cerebral Venous Thrombosis (CVT). |
| **Treatment** | Initiated based on CVT diagnosis. |

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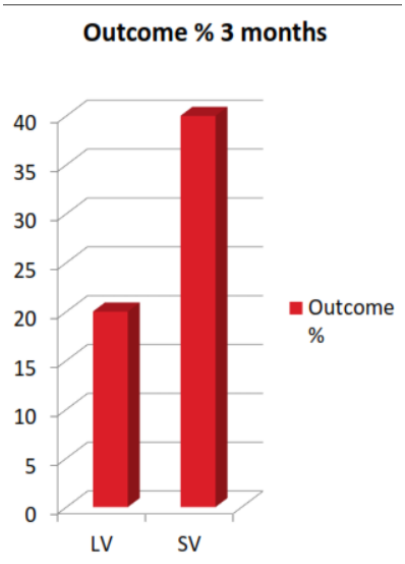
# STROKE

| | |
|---|---|
| **Definition** | Acute or sudden onset of neurological deficits lasting at least 24 hours due to a vascular mechanism. |
| **Incidence** | 250 per 100,000 population |
| **New Cases Per Year** | 35,000 |

## Ischemic Stroke

An ischemic stroke occurs when a blood clot or plaque blocks a blood vessel in the brain, cutting off blood flow and causing brain tissue damage

| Category | Description |
|---|---|
| **Large Vessel** | Involves major brain arteries. |
| **Small Vessel** | Affects smaller penetrating arteries. |
| **Others** | Various uncommon causes. |




## Outcomes of Ischemic Stroke (After 3 Months)

| Stroke Type | Outcome % |
|---|---|
| **Large Vessel (LV)** | 40% |
| **Small Vessel (SV)** | 25% |

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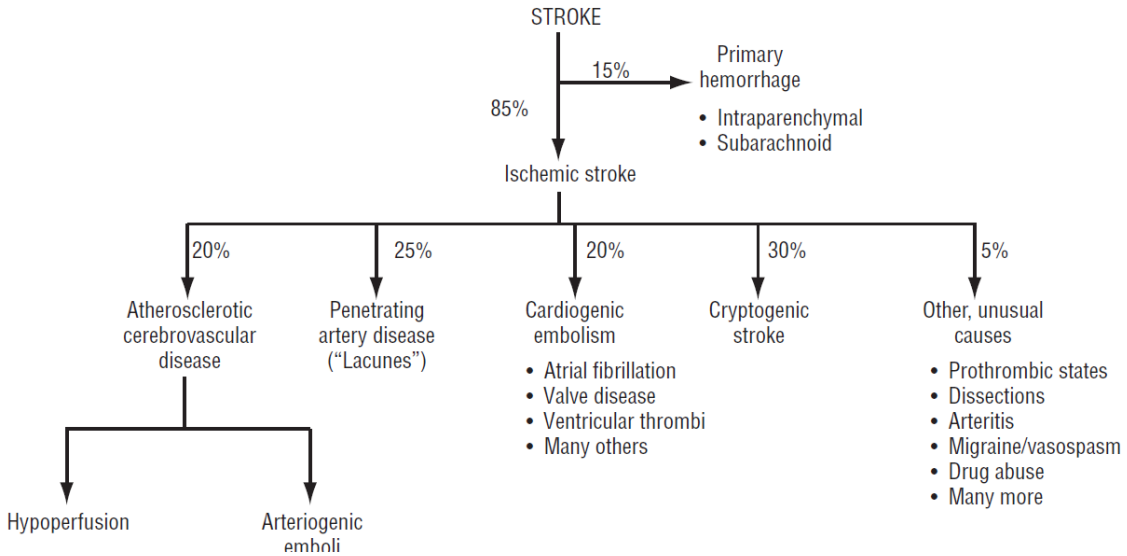
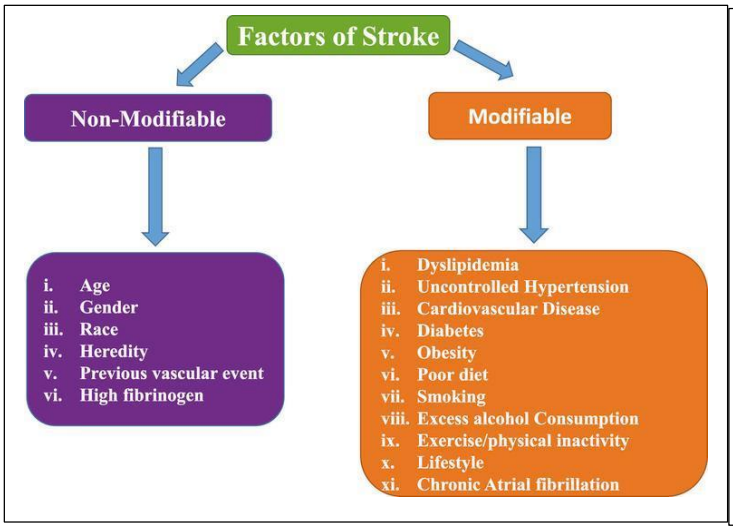
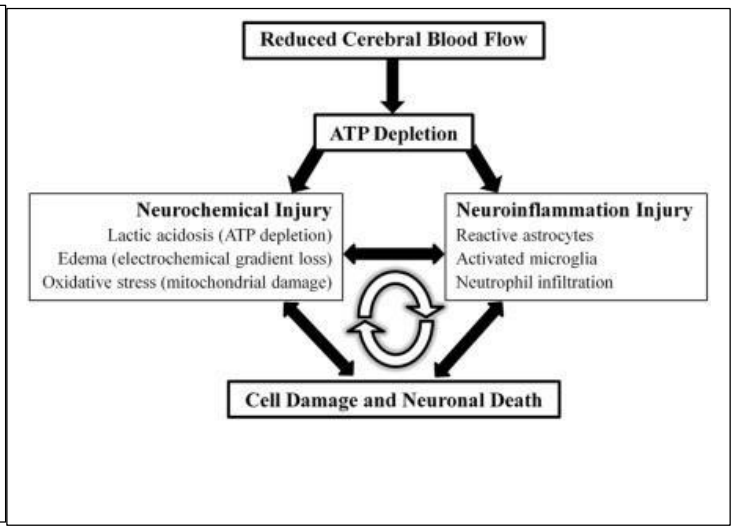
# Classification:




## Risk factors Ischemic stroke




## Pathophysiology ischemic stroke

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## Diagnosis & Classification of Stroke

- **Large Vessel Stroke**
  - Involves major arteries (e.g., MCA, ACA, PCA, Basilar artery)
  - Symptoms depend on affected artery
- **Small Vessel Stroke (Lacunar Stroke)**
  - Affects smaller penetrating arteries
  - Can cause pure motor or sensory deficits

---

## Major Arteries and Their Infarctions

| Artery | Affected Areas | Clinical Features |
|---|---|---|
| **Middle Cerebral Artery (MCA)** | Lateral frontal, temporal, parietal lobes | Hemiparesis, aphasia, visual deficits |
| **Anterior Cerebral Artery (ACA)** | Medial frontal & parietal lobes | Contralateral leg weakness |
| **Posterior Cerebral Artery (PCA)** | Occipital lobe, thalamus | Visual impairment, memory issues |
| **Basilar Artery** | Brainstem, cerebellum | CN deficits, coma, instability |
| **Small Cerebral Blood Vessels (Lacunar Stroke)** | Internal capsule, thalamus, pons | Pure motor or sensory stroke |

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## Middle Cerebral Artery (MCA) Stroke

- **Symptoms**:
  - Contralateral weakness
  - Sensory loss
  - Aphasia (if dominant hemisphere affected)
  - Hemineglect (if non-dominant hemisphere affected)
  - Visual field defects
- **Complete MCA Syndrome**:
  - Severe motor & sensory loss
  - Global aphasia (if left hemisphere affected)
  - Hemispatial neglect (if right hemisphere affected)

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## Anterior Cerebral Artery (ACA) Stroke

- **Contralateral leg weakness**
- **Less involvement of arms & face**
- **Possible behavioral and cognitive changes**

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## Posterior Cerebral Artery (PCA) Stroke

- **5-10% of all strokes**
- **Symptoms**:
  - Visual field deficits
  - Memory disturbances
  - Sensory impairments

---

### Basilar Artery Stroke

- **Symptoms**:
  - Cranial nerve deficits
  - Apnea (breathing issues)
  - Systemic instability
  - Coma

---

### Small Vessel (Lacunar) Strokes

- **Types**:
  - **Pure Motor Stroke**
  - **Pure Sensory Stroke**
  - **Lacunar Infarcts** (small deep infarctions)
- **Commonly affected arteries**:
  - Lenticulostriate arteries

### Thalamogeniculate & Thalamoperforator Artery Stroke

| Artery | Affected Brain Region | Clinical Features |
|---|---|---|
| **Thalamogeniculate Arteries** | Lateral thalamus | - **Pure sensory stroke** (contralateral sensory loss) |
| **Thalamoperforator Arteries** | Medial thalamus, midbrain | - **Cognitive & memory impairments**<br>- **Decreased consciousness**<br>- **Motor deficits (if midbrain involved)** |

---

# Ischemic Stroke: Treatment Options

## 1. Lifestyle Modifications

- Avoid Smoking
- Healthy Eating Habits
- Regular Physical Activity
- Stress-Free Life
- Maintain Healthy Body Weight
- Blood Pressure (BP) Control
- Compliance with Medications
- Emotional Support

## 2. Goals of Ischemic Stroke Treatment

- Reduce ongoing neurological injury.
- Prevent complications due to immobility and neurological dysfunction.
- Prevent stroke recurrence.
- Decrease mortality and long-term disability.

## 3. Non-Pharmacological Treatment

| Procedure | Purpose |
|---|---|
| **Craniectomy** | Used in case of cerebral edema. |
| **Carotid Endarterectomy** | Removes plaque from carotid artery. |
| **Carotid Stenting** | Keeps carotid artery open. |

## 4. Pharmacological Treatment

| Drug | Dosage & Timing | Effectiveness |
|---|---|---|
| **Tissue Plasminogen Activator (tPA)** | 0.9 mg/kg over 1 hour (10% as bolus over 1 minute) | |
| **tPA within <3 hrs** | 75% good outcomes within 6 months | |
| **tPA within 3-4.5 hrs** | 26% good outcomes | |
| **tPA after >4.5 hrs** | 15% good outcomes | |
| **Aspirin** | 300 mg after 24 hours | Prevents clot progression |

## 5. Inpatient Management

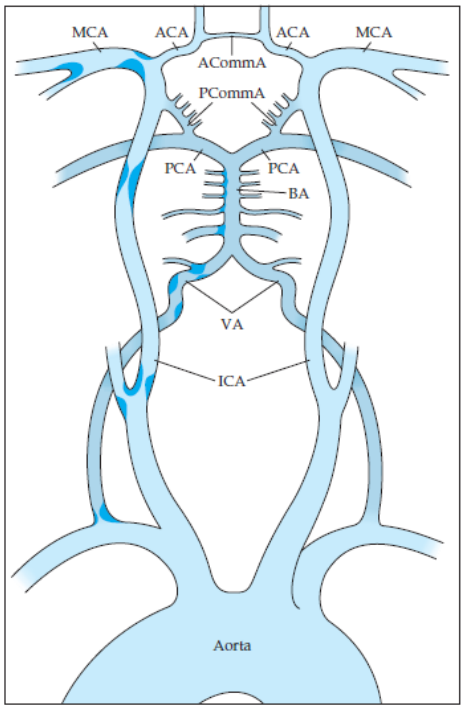
| Condition | Management |
|---|---|
| **Hyperthermia** | Antipyretics |
| **Hyperglycemia** | Insulin |
| **Hypertension** | ACE Inhibitors (ACEI), ARBs, Diuretics |
| **Respiratory Issues** | Oxygen Therapy |
| **Dysphagia** | Nasogastric (NG) Tube |
| **Infections** | Antibiotics |
| **Brain Swelling** | Corticosteroids |

---

# Hemorrhagic Stroke Treatment

| Treatment | Purpose |
|---|---|
| **Blood Pressure Control** | Prevent further bleeding |
| **Surgical Evacuation** | Removes hematoma |
| **Reducing Intracranial Pressure (ICP)** | Manages brain swelling |
| **Ventricular Drainage** | Reduces CSF buildup |
| **Surgical Clipping** | Within 72 hours of onset |
| **Triple H Therapy** | Hypertension, Hypervolemia, Hemodilution |

## Cerebrovascular anatomy and common sites of atherosclerosis




| Category | Primary Agents | Alternatives |
| --- | --- | --- |
| **Acute Treatment** | - tPA 0.9 mg/kg IV (max 90 kg) over 1 hour (within 3 hours of onset) - ASA 160–325 mg daily (within 48 hours of onset) | - tPA (various doses) intra-arterially (up to 6 hours after onset) |
| **Secondary Prevention** | | |
| **Noncardioembolic Stroke** | - Aspirin 50–325 mg daily - Clopidogrel 75 mg daily - Aspirin 25 mg + Extended-release dipyridamole 200 mg twice daily | - Ticlopidine 250 mg twice daily |
| **Cardioembolic Stroke** (esp. Atrial Fibrillation) | - Warfarin (INR = 2.5) | |
| **All Stroke Patients** | - ACE inhibitor + diuretic or ARB (for blood pressure lowering) – Statin | |

# Epilepsy

## Seizures

- Seizures are caused by **transient (temporary), paroxysmal (sudden), and synchronous (simultaneous)** discharges of groups of neurons in the brain.
- Results in changes in **behavior, movements, feelings, or levels of consciousness**.
- Causes include:
  - **Hypoglycemia** (low blood sugar)
  - **Hyponatremia** (low sodium levels)
  - **Drug toxicity**
- May result in only a **single seizure or a few seizures at most**.
- Treatment of the **underlying abnormality** corrects the seizure disorder.

---

## Epilepsy

- Epilepsy is **recurrent (repeated) seizures**.
- Incidence is **high in infancy and old age** but decreases during childhood, reaching its lowest in adolescence.
- **May be hereditary or acquired:**

| Type of Epilepsy | Causes |
|---|---|
| **Hereditary** | May be due to **channelopathies** (genetic defects affecting ion channels) |
| **Acquired** | Due to **head trauma, CNS infection, structural brain malformations, strokes, or cerebral neoplasm (brain tumor)** |

---

## Pathophysiology

- **Unstable cell membrane** or its surrounding supportive cells.
- **Excitatory (glutamatergic signaling)** and **inhibitory (GABAergic signaling)** imbalance.
- Normal neuronal activity depends on:
  - **Glucose, oxygen, sodium, potassium, chloride, calcium, pH, and amino acids.**
- **Increased oxygen levels → ischemia (reduced blood supply) → cognitive abnormality (mental dysfunction).**
- Abnormal electrical activity **spreads through physiological pathways** to adjacent or distant brain areas.
- **Clinical manifestations depend on:**
  - Site of the seizure focus
  - Degree of surrounding brain irritability
  - Intensity of the impulse
  - **Raising threshold (increasing resistance to seizure activity) and limiting wave propagation (spread of abnormal signals).**

# Classification of Epileptic Seizures

1. **Partial Seizures (Focal Seizures)**
2. **Generalized Seizures**
3. **Unclassified Seizures**

---

# 1. Partial (Focal) Seizures

- **Originate in one hemisphere of the brain**.
- Result in **asymmetric (unequal) motor symptoms**.

### a. Simple Partial Seizures

- **Originate in the neocortex**.
- **Consciousness remains intact**.
- Symptoms:

| Symptom Type | Example |
|---|---|
| **Motor** | Focal myoclonus (muscle jerking) of a limb, hand, or face |
| **Sensory** | Seeing colored spots or lines |
| **Autonomic** | Epigastric sensation (abdominal discomfort) |
| **Psychic** | Memory disturbances |

### b. Complex Partial Seizures

- **Alteration of consciousness**.
- **Arrest of motion (sudden pause in activity)**.
- **Automatisms (involuntary movements)** like:
    - Simple hand movements
    - Oroalimentary (mouth-related) behavior like tasting movements or swallowing
    - Verbal utterances
    - **Amnesia (memory loss)**.
- **Postictal (after-seizure) effects**.
- **Aura (warning signs like sensory, autonomic, or psychic symptoms) precedes loss of consciousness.**

---

# 2. Generalized Seizures

- **Loss of consciousness** with **apnea (temporary breathing pause)** and **violent muscle contractions**.
- Patients may experience:

    - **Mouth trauma**
    - **Bladder incontinence (loss of bladder control)**
    - **Salivation (excessive drooling)**
    - Increased **pulse rate and blood pressure** during the seizure.
- **Phases of Generalized Seizure:**

| Phase | Description |
|---|---|
| **Tonic Phase** | Stiffening of muscles |
| **Clonic Phase** | Rhythmic muscle jerking |
| **Postictal Phase** | Breathing resumes, followed by unresponsiveness and gradual recovery |

- **Postictal symptoms**:
    - Confusion for several minutes or longer
    - Muscle pain and headache
    - **Stereotyped behavior (predictable pattern of post-seizure recovery)**

---

## Types of Generalized Seizures

| Type | Description |
|---|---|
| **a. Absence Seizures** | Brief loss of awareness without convulsions |
| **b. Myoclonic Seizures** | Sudden, brief muscle jerks |
| **c. Clonic Seizures** | Repetitive rhythmic jerking movements |
| **d. Tonic-Clonic Seizures** | Stiffening followed by rhythmic jerking |
| **e. Atonic Seizures** | Sudden loss of muscle tone, causing falls |

---

# Diagnosis

| Test | Purpose |
|---|---|
| **HX (History)** | Patient's medical and seizure history |
| **CT (Computed Tomography)** | Brain imaging to detect structural abnormalities |
| **MRI (Magnetic Resonance Imaging)** | Detailed brain imaging for lesions or malformations |
| **CSF (Cerebrospinal Fluid Analysis)** | To rule out infections or inflammatory causes |
| **Prolactin** | Elevated post-seizure; helps differentiate from psychogenic seizures |
| **EEG (Electroencephalogram)** | Detects abnormal electrical activity in the brain |

---

# Treatment

## Treatment Goals

- **Seizure-free state**
- **Good quality of life**
- **Reduced side effects**
- **Sacrifice of seizure control** (in some cases where side effects outweigh benefits)
- **Concerns related to:**
    - Driving
    - Future planning
    - Relationships
    - Safety
    - Social isolation & stigma
- **Neuropsychiatric comorbidities** may accompany epilepsy

---

## Treatment Options

1. **AEDs (Antiepileptic Drugs)**
2. **Vagus Nerve Stimulation**
3. **Surgery**
4. **Ketogenic Diet**

---

# 1. Antiepileptic Drugs (AEDs)

- **30% to 35%** of patients will be **refractory (resistant) to treatment**.
- Goals should shift to **decreasing seizure frequency** and **minimizing drug adverse effects**.
- **Monotherapy (single drug treatment) is preferred**:
    - **50% to 70%** of patients can be maintained on one drug.
- **Prognosis for 12-month seizure freedom with monotherapy:**

| Seizure Type | Success Rate |
|---|---|
| **Generalized Tonic-Clonic (GTC) Seizures** | 48% to 55% |
| **Complex Partial Seizures** | 23% to 26% |
| **Mixed Seizure Types** | 25% to 32% |

---

## 2. AED Usage Guidelines

- **Patients with ≥2 seizures** should **start AED therapy**.
- **AED withdrawal** requires a **seizure-free period of 2 to 4 years**.
- **First-line AEDs for new-onset seizures:**

| Seizure Type | Drug of Choice |
|---|---|
| **Partial or Generalized Seizures** | Carbamazepine, Phenytoin |
| **Primary Generalized Convulsions** | Valproate, Lamotrigine, Topiramate |
| **Absence Seizures** | Ethosuximide |
| **Absence Seizures + Generalized Convulsions/Myoclonic Seizures** | Valproate |

- If the **first drug fails**, **increase the dose** before opting for a second AED.

---

## Drugs of Choice for Specific-Seizure Disorders

| Seizure Type | First-Line Drugs | Alternative Drugs |
|---|---|---|
| Partial seizures | Carbamazepine<br>Phenytoin<br>Lamotrigine<br>Valproic acid<br>Oxcarbazepine | Gabapentin<br>Topiramate<br>Levetiracetam<br>Zonisamide<br>Tiagabine<br>Primidone, phenobarbital<br>Felbamate |
| Generalized seizures | | |
| Absence | Valproic acid, ethosuximide | Lamotrigine, levetiracetam |
| Myoclonic | Valproic acid, clonazepam | Lamotrigine, topiramate, felbamate, zonisamide, levetiracetam |
| Tonic-clonic | Phenytoin, carbamazepine, valproic acid | Lamotrigine, topiramate, phenobarbital, primidone, oxcarbazepine, levetiracetam |

# Vagus Nerve Stimulation (VNS)

### Criteria for VNS Placement

- **Indicated for partial-onset seizures** that persist despite **adequate trials of two or three AEDs**.
- The patient **should not be a good candidate for focal resective surgery**.
- **Patients should be older than 12 years**.

---

# Surgery

| Criteria | Details |
|---|---|
| **Focus is difficult to locate** | Surgery is considered when the exact seizure focus is unclear. |
| **Most common procedure** | **Temporal lobectomy** (removal of part of the temporal lobe). |
| **Success Rate** | **- 70% remain seizure-free**. |

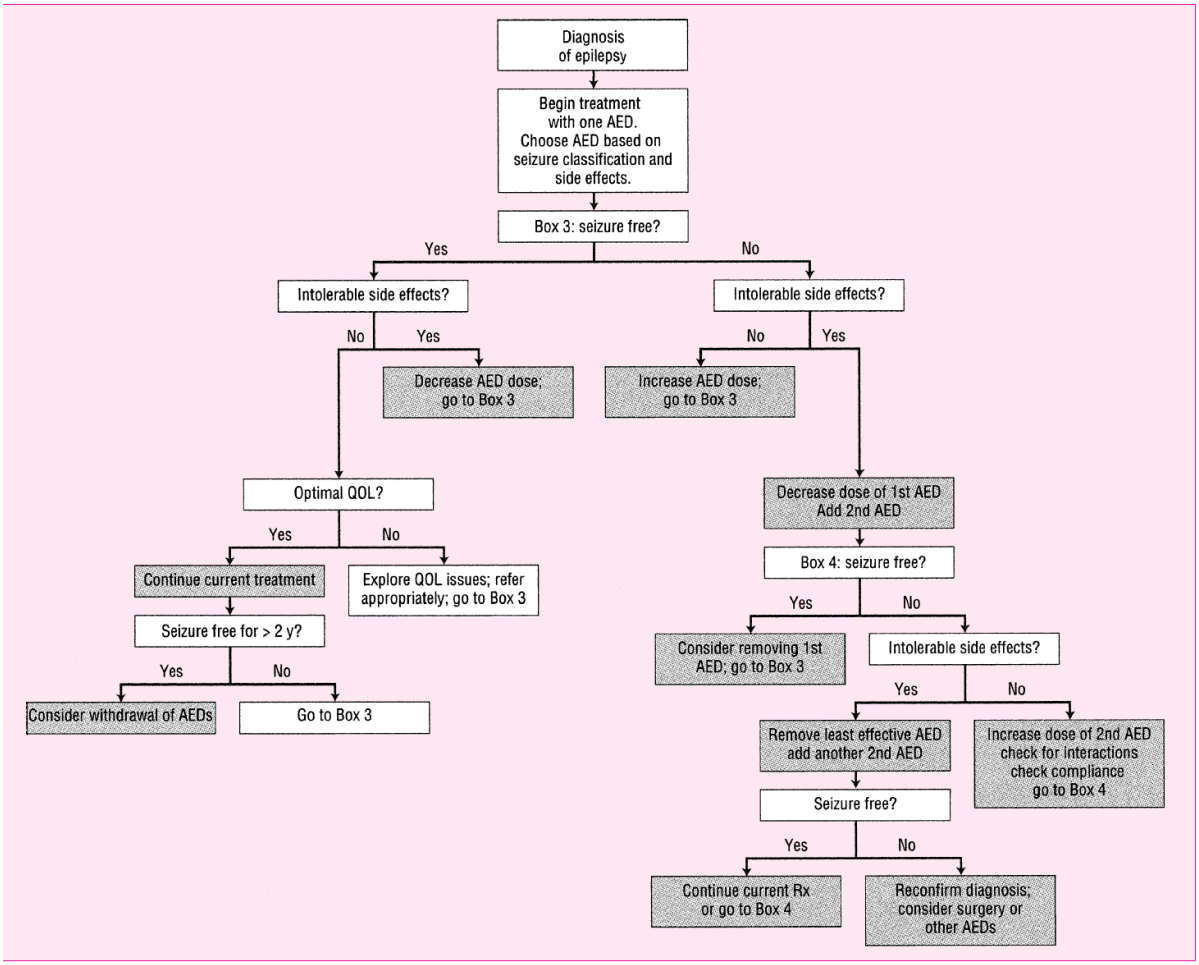
- **20% show marked improvement**. |

---

# Ketogenic Diet

- A **high-fat, low-carbohydrate diet** that prevents seizures by **maintaining the patient in ketosis** (a metabolic state where the body burns fat for energy).
- **Diet composition:**

| Nutrient | Ratio |
|---|---|
| **Fats** | 4 parts |
| **Proteins + Carbohydrates** | 1 part |



# **Psychosis** (CNS Disorders - Chapter 10, Unit V)

## Definition

Psychosis is a mental condition where a person struggles to differentiate between reality and delusions or hallucinations.

## Symptoms

| Category | Symptoms |
|---|---|
| **Positive Symptoms** (Excess of normal functions) | - Hallucinations (seeing or hearing things that aren't there)<br>- Delusions (false beliefs)<br>- Disorganized speech |
| **Negative Symptoms** (Reduction of normal functions) | - Blunted affect (reduced emotional expression)<br>- Poverty of thoughts (limited speech and ideas)<br>- Lack of emotions<br>- Anhedonia (inability to feel pleasure) |
| **Cognitive Symptoms** (Thinking difficulties) | - Inattention (trouble focusing)<br>- Impaired memory<br>- Illogical thinking<br>- Poor judgment |

---

# Types of Psychosis

## 1. Affective Psychosis (Mood-Related Psychosis)

Psychosis occurs as part of a mood disorder, such as depression or bipolar disorder.

| Type | Description |
|---|---|
| **Schizoaffective Disorder** | A combination of schizophrenia symptoms and mood disorder (either depression or bipolar disorder). |
| **Bipolar Disorder with Psychotic Features** | Psychotic symptoms appear during manic or depressive episodes. |
| **Depression with Psychotic Features** | Severe depression accompanied by hallucinations or delusions. |

## 2. Non-Affective Psychosis (Not Directly Related to Mood Disorders)

Psychosis occurs independently of mood disorders.

| Type | Description |
|---|---|
| **Schizophrenia** | A chronic mental disorder with hallucinations, delusions, and impaired thinking. |
| **Schizophreniform Disorder** | Similar to schizophrenia but lasts less than six months. |
| **Borderline Personality Disorder (BPD) with Psychotic Episodes** | Brief psychotic episodes, often triggered by stress. |
| **Drug-Induced Psychosis** | Caused by the use of substances such as LSD, cocaine, or methamphetamine. |
| **Non-Affective Psychosis** | Psychosis not linked to mood disorders, often due to neurological or unknown causes. |

---

# Pathophysiology of Psychosis

- **Reduction in Grey Matter Volume** – Loss of brain tissue affecting cognition and emotions.
- **MRI Findings** – Overall reduction in brain mass and cortex size.
- **Decreased Cortical Thickness** – Thinning of the brain's outer layer, impacting thought processes.
- **Variations in Regional Cerebral Blood Flow (rCBF)** – Uneven blood supply to different brain regions.
- **Neurotransmitter Imbalance:**
    - **Increased Dopamine (D2 Receptor Activation)** – Causes hallucinations and delusions.
    - **Decreased Dopamine (D1 Activity)** – Leads to cognitive impairment and reduced motivation.
    - **Increased Serotonin (5HT)** – May contribute to positive symptoms like hallucinations.

---

# Signs and Symptoms of Psychosis

## 1. Positive Symptoms (Excess or Distorted Functions)

| Symptom | Description |
|---|---|
| **Hallucinations** | Seeing, hearing, or feeling things that aren't there. |
| **Delusions** | Strong false beliefs not based on reality. |
| **Disorganized Speech** | Talking in a confused or illogical way. |

## 2. Negative Symptoms (Loss of Normal Functions)

| Symptom | Description |
|---|---|
| **Blunted Affect** | Reduced emotional expression. |
| **Poverty of Thoughts** | Limited speech and ideas. |
| **Lack of Emotions** | Decreased ability to express feelings. |
| **Anhedonia** | Inability to feel pleasure. |

## 3. Cognitive Symptoms (Thinking Difficulties)

| Symptom | Description |
|---|---|
| **Inattention** | Difficulty focusing or concentrating. |
| **Impaired Memory** | Trouble remembering information. |
| **Illogical Thinking** | Inability to form rational thoughts. |
| **Impaired Judgment** | Poor decision-making skills. |

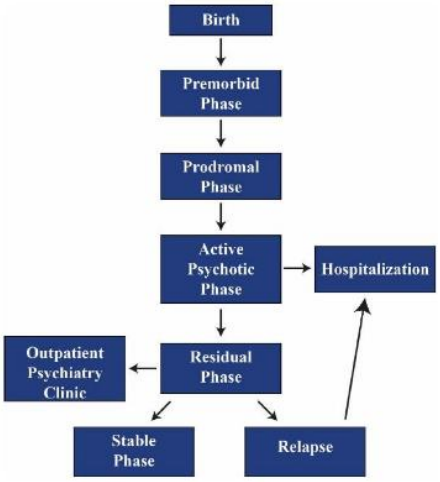


Figure 1-2: Course and prognosis of Schizophrenia

---

# Etiology (Causes of Psychosis)

1. **Normal States** – Temporary psychosis due to sleep deprivation, extreme stress, or sensory deprivation.
2. **Trauma** – Psychological or physical trauma, such as childhood abuse or accidents.
3. **Psychiatric Disorders** – Conditions like schizophrenia, bipolar disorder, and severe depression.
4. **Secondary Causes** – Brain injuries, infections, metabolic disorders, or neurological conditions.
5. **Psychoactive Drugs** – Substance-induced psychosis from drugs like LSD, cocaine, or alcohol.

---

# Diagnosis of Psychosis

| Step | Tests/Evaluations |
|---|---|
| **1. Exclude Other Causes** | Ensure symptoms are not due to medical conditions. |
| **2. Laboratory Tests** | CBC (Complete Blood Count), TFTs (Thyroid Function Tests), ESR (Erythrocyte Sedimentation Rate), Electrolytes. |
| **3. Brain Imaging** | MRI, CT scan to detect structural abnormalities. |
| **4. Clinical Evaluation** | Detailed interview and Mental Status Examination (MSE). |
| **5. Psychosis Rating Scales** | BPRS (Brief Psychiatric Rating Scale), PANSS (Positive and Negative Syndrome Scale). |

---

# Management Plan

### Multidisciplinary Approach

- **Psychiatrists** – Diagnose and prescribe medications.
- **Psychotherapists** – Provide therapy and counseling.
- **Social Workers & Nursing Staff** – Support patient care and rehabilitation.

### Treatment Phases

| Phase | Goal |
|---|---|
| **Short-Term** | Stabilize the patient, reduce symptoms, and ensure safety. |
| **Long-Term** | Prevent relapse, improve daily functioning, and provide continued therapy. |

---

# Pharmacological Management

**Goal:** Treat positive and negative symptoms, improve cognitive function, and prevent hospitalization/relapse.

| Category | Description |
|---|---|
| **FGA (First-Generation Antipsychotics)** | Older drugs mainly targeting positive symptoms. |
| **SGA (Second-Generation Antipsychotics)** | Newer drugs with fewer side effects, treating both positive and negative symptoms. |
| **Combination Therapy** | Using multiple drugs if needed. |
| **Augmentation Therapy** | Adding antidepressants or mood stabilizers for better control. |

---

**Table 1-1: Antipsychotic(s) type and comparative risk of EPS and obesity(3**

| Antipsychotic | EPS[a] | Obesity |
|---|---|---|
| **FGA(s)[b]** | | |
| *Chlorpromazine* | + + + | + + |
| *Fluphenazine* | + + + + | + |
| *Haloperidol* | + + + + | + |
| *Perphenazine* | + + + + | + |
| *Thioridazine* | + + + | + |
| *Thiothixene* | + + + + | + |
| **SGA(s)[c]** | | |
| *Olanzapine* | + + | + + + + |
| *Clozapine* | + | + + + + |
| *Risperidone* | + + | + + |
| *Quietipine* | + | + + |
| *Aripiprazole* | + | + |
| *Ziprasidone* | ++ | + |

# Meningitis

### Definition:

Meningitis is an inflammation of the meninges, the protective membranes covering the brain and spinal cord.

### Types of CNS Infections:

- **Meningitis** – Inflammation of the meninges.
- **Encephalitis** – Inflammation of the brain.

### Prevalance:

- **0.5 million** people affected worldwide each year.
- **137 deaths** occur daily.
- In **Pakistan**, around **23,000 children** die from meningitis each year.

---

## Classification of Meningitis

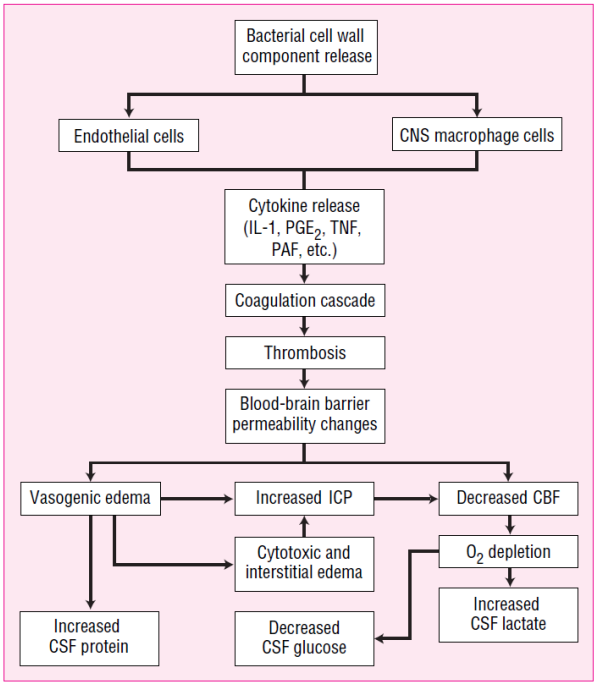
| Category | Type | Description |
|---|---|---|
| **Based on Cause of Infection** | **Acquired Meningitis** | Caused by infections from the environment or invasive medical procedures. |
| **Based on Anatomy Affected** | **Pachymeningitis** | Affects the **dura mater** (outer membrane). |
| | **Leptomeningitis** | Involves the **arachnoid mater** and **subarachnoid space** (inner membranes). |
| **Based on Cause (Etiology)** | **Bacterial Meningitis** | Caused by bacteria (*Streptococcus pneumoniae*, *Neisseria meningitidis*). |
| | **Viral Meningitis** | Caused by viruses (e.g., enteroviruses, herpes simplex virus). |
| | **Non-Infectious Meningitis** | Caused by conditions like autoimmune diseases, cancer, or medication reactions. |

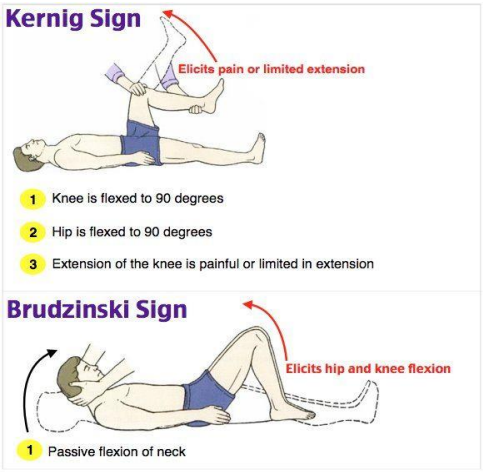
---

## Pathophysiology of Meningitis

1. **Entry of Pathogen:**
    - The infectious organism originates from colonies elsewhere in the body.
    - It invades the **submucosa**, bypassing the body's immune defenses.
    - Reaches the **central nervous system (CNS)** through:
        - **Bloodstream (Hematogenous spread)**
        - **Retrograde neuronal access** (via nerves)
        - **Contiguous spread** (from nearby infections like sinusitis, otitis media).

2. **Invasion & Immune Response:**
    - The bacteria penetrate the **blood-brain barrier (BBB)**, disrupting its function.
    - The immune system responds, leading to **inflammation and infection** in the meninges.
3. **Physiological Changes & Damage:**
    - **Leaky blood vessels** → Increased permeability.
    - **White blood cell (WBC) infiltration** → Further inflammation.
    - **Brain swelling (edema)** → Increased intracranial pressure (ICP).
    - **Reduced cerebral blood flow (crBF)** → Oxygen deprivation to brain tissues.
4. **Complications:**
    - **Cranial nerve (CN) damage** → Neurological deficits.
    - **Obliteration of cerebrospinal fluid (CSF) pathways** → Hydrocephalus.
    - **Vasculitis and thrombophlebitis** → Blood vessel inflammation and clotting.
    - **Types of Edema:**
        - **Vasogenic edema** (due to leaky capillaries).
        - **Interstitial edema** (CSF accumulation).
        - **Cytotoxic edema** (cellular swelling).
5. **Clinical Symptoms:**
    - Headache
    - Neck stiffness
    - Fever
    - Photophobia (light sensitivity)
    - Septicemia (blood infection)




# Clinical Presentation of Meningitis

| Category | Symptoms |
|---|---|
| **General Symptoms** | Fever, headache, neck stiffness |
| **Neurological Symptoms** | Altered mental status, confusion, delirium, sleepiness, coma |
| **Sensory Symptoms** | Photophobia (sensitivity to light) |

# Diagnosis of Meningitis

### 1. Physical Examination

- **Kernig's Sign:** Resistance and pain when extending the knee with the hip flexed.
- **Brudzinski's Sign:** Involuntary bending of the knees when lifting the head while lying down.

### 2. Laboratory Tests

| Test | Purpose |
|---|---|
| **Blood Investigations (BLIs)** | General infection markers |
| **Complete Blood Count (CBC)** | Checks for elevated white blood cells (WBCs) |
| **Blood Glucose** | Low levels may indicate bacterial meningitis |
| **Electrolytes** | Assesses metabolic imbalances |
| **Blood Culture** | Identifies causative bacteria (50% positivity rate) |
| **Serum Procalcitonin** | High levels indicate bacterial meningitis |

---

## Cerebrospinal Fluid (CSF) Findings in Different Types of Meningitis

| Cause | Appearance | Polymorphonuclear Cells | Lymphocytes | Protein | Glucose |
|---|---|---|---|---|---|
| **Pyogenic (Bacterial) Meningitis** | Yellowish, turbid | Markedly increased | Slightly increased or Normal | Markedly increased | Decreased |
| **Viral Meningitis** | Clear fluid | Slightly increased or Normal | Markedly increased | Slightly increased or Normal | Normal |
| **Tuberculous Meningitis** | Yellowish, viscous | Slightly increased or Normal | Markedly increased | Increased | Decreased |
| **Fungal Meningitis** | Yellowish, viscous | Slightly increased or Normal | Markedly increased | Slightly increased or Normal | Normal or Decreased |

---

# Management of Meningitis - Goals of Treatment:

1. **Eradicate the infectious agent** (bacteria/virus).
2. **Relieve symptoms** (fever, headache, neck stiffness).
3. **Prevent neurological complications** (seizures, brain damage).

---

### Supportive Management:

| Treatment | Purpose |
|---|---|
| **Antipyretics** | Reduce fever and discomfort. |
| **IV Fluids** | Manage **hypotension and shock**. |
| **Oxygen Therapy** | Ensure adequate oxygen supply to the brain. |
| **Benzodiazepines / Barbiturates** | Control **seizures**. |
| **Furosemide / Mannitol** | Reduce **intracranial pressure (ICP)**. |
| **Corticosteroids (Dexamethasone)** | Reduce **inflammation and brain swelling**. |

**TABLE 105–2. Bacterial Meningitis: Most Likely and Empirical Therapy by Age Group**

| Age Commonly Affected | Most Likely Organisms | Empirical Therapy | Risk Factors for All Age Groups |
|---|---|---|---|
| Newborn–1 month | Gram-negative enterics[a]<br>Group B *Streptococcus*<br>*Listeria monocytogenes* | Ampicillin + cefotaxime or ceftriaxone or aminoglycoside | Respiratory tract infection<br>Otitis media<br>Mastoiditis<br>Head trauma<br>Alcoholism<br>High-dose steroids |
| 1 month–4 years | *H. influenzae*<br>*N. meningitidis*<br>*S. pneumoniae* | Cefotaxime or ceftriaxone and vancomycin[b] | Splenectomy<br>Sickle cell disease<br>Immunoglobulin deficiency |
| 5–29 years | *N. meningitidis*<br>*S. pneumoniae*<br>*H. influenzae* | Cefotaxime or ceftriaxone and vancomycin[b] | Immunosuppression |
| 30–60 years | *S. pneumoniae*<br>*N. meningitidis* | Cefotaxime or ceftriaxone and vancomycin[b] | |
| >60 years | *S. pneumoniae*<br>Gram-negative enterics<br>*L. monocytogenes* | Ampicillin + cefotaxime or ceftriaxone or aminoglycoside and vancomycin[b] | |

[a] *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp. common.
[b] Vancomycin use should be based on local incidence of penicillin-resistant *S. pneumoniae* and until cefotaxime ceftriaxone minimum inhibitory concentration results are available.

**TABLE 105–2. Bacterial Meningitis: Most Likely and Empirical Therapy by Age Group**

| Age Commonly | Most Likely | Risk Factors for |
|---|---|---|

**TABLE 105–4. Antimicrobial Agents of First Choice and Alternative Choice in the Treatment of Meningitis Caused by Gram-Positive Microorganisms**

| Organism | Antibiotic of First Choice[a] | Alternative Antibiotics[a] |
|---|---|---|
| *Streptococcus pneumoniae* | | |
| Penicillin susceptible | Penicillin G 200,000–300,000 units/kg/day every 4 h IV; max: 4 million units every 4 h IV | Cefotaxime 200 mg/kg/day every 4–6 h IV; max: 2 g every 4 h<br>Ceftriaxone 100 mg/kg/day every 24 h IV[b]; max: adults 2 g every 12 h<br>Chloramphenicol[e] 100 mg/kg/day every 6 h; max: 1.5 g every 6 h |
| Penicillin resistant[c] | Cefotaxime or ceftriaxone and vancomycin[e] 30–40 mg/kg/day IV (60 mg/kg/day IV every 6 h[b]) | Cefepime 50 mg/kg/dose every 12 h[b]; max: adult 2 g every 8 h IV<br>Or meropenem 40 mg/kg every 8 h IV[b]; max: adults 1 g every 8 h IV with vancomycin[e]<br>Linezolid 600 mg every 12 h IV[d] |
| Group B *Streptococcus* | Penicillin ± gentamicin[e] | Ampicillin ± gentamicin[e]<br>Cefotaxime<br>Ceftriaxone<br>Chloramphenicol[e] |
| *Staphylococcus aureus* | | |
| Penicillin resistant | Nafcillin 200 mg/kg/day every 4 h IV; max: 2 g every 4 h IV | Vancomycin[e] |
| Methicillin resistant | Vancomycin[e] | Linezolid[d] |
| *Staphylococcus epidermidis* | | |
| Penicillin resistant | Nafcillin | Vancomycin[e] |
| Methicillin resistant | Vancomycin[e] | Linezolid[d] |
| *Listeria monocytogenes* | Ampicillin 220–400 mg/kg/day, every 6 h IV or penicillin G max: 2 g every 4 h IV plus gentamicin[e] | Trimethoprim 10 mg/kg/day and sulfamethoxazole 50 mg/kg/day, every 6 h |
| *Bacillus anthracis* | A consensus regarding recommended agents for the treatment of CNS infections caused by anthrax or other biologic warfare agents has not been reached. Optimal treatment must be tailored to the particular pathogen and/or genetic variants of the pathogen. | |

[a] Recommended doses for adults and pediatric patients with normal renal and/or hepatic function.
[b] Pediatrics.
[c] Incidence of resistance is 20% to 45% worldwide.
[d] Clinical data are lacking, but linezolid may offer an alternative for the treatment of such infections.
[e] Monitor drug levels in serum.

**TABLE 105–5. Antimicrobial Agents of First Choice and Alternative Choice in the Treatment of Meningitis Caused by Gram-Negative Microorganisms**

| Organism | Antibiotic of First Choice[a] | Alternative Antibiotics[a] |
|---|---|---|
| *Neisseria meningitis* (meningococcal) | Penicillin G 200,000–300,000 units/kg/day | Cefotaxime 200 mg/kg/day every 4 h; max: 2 g IV every 4 h<br>Ceftriaxone 100 mg/kg/day every 24 h[b]; max: adults 2 g IV every 12 h<br>Chloramphenicol[e] 100 mg/kg/day every 6 h; max: 1.5 g IV every 6 h |
| *Escherichia coli* | Cefotaxime or ceftriaxone | Cefepime 50 mg/kg/dose every 12 h[b]; max: adult 2 g every 8 h IV<br>Meropenem 40 mg/kg every 8 h IV[b]; max: adults 1 g every 8 h IV |
| *Hemophilus influenzae* | | |
| β-Lactamase positive | Cefotaxime | Ceftriaxone |
| β-Lactamase negative | Ampicillin 200–400 mg/kg/day every 6 h IV; max: 2 g every 4 h IV | Cefotaxime<br>Ceftriaxone |
| *Pseudomonas aeruginosa* | Ceftazidime 85 mg/kg/day; max: 2 g IV every 6 h plus tobramycin[e] 5–7.5 mg/kg/day IV[c] | Meropenem<br>Piperacillin 200–300 mg/kg/day; max: 3 g every 4 h IV plus tobramycin[e]<br>Colistin sulfomethate[e] 5 mg/kg/day IV[d] |
| Enterobacteriaceae | Cefotaxime | Ceftriaxone<br>Piperacillin plus aminoglycoside[e]<br>Meropenem |



[a] Recommended doses for adults and pediatric patients with normal renal and/or hepatic function.

# Pulmonary Tuberculosis (TB)

Overview & Case Study

## 1. Case Study: Jamil Khan

### Patient Information

| Detail | Description |
|---|---|
| **Name** | Jamil Khan |
| **Age** | 32 years |
| **Gender** | Male |
| **Medical History** | Mother died due to TB |
| **Occupation** | Studying for Provincial Management Services Exam |

### Symptoms (Since Last Week)

- Cough
- High-grade fever
- Night sweats
- Vomiting

### Investigations & Findings

| Test | Results |
|---|---|
| **IV Cephalosporins Response** | Patient remained febrile |
| **ESR & CRP** | Elevated (indicating inflammation/infection) |
| **Chest X-ray & Chest U/S** | Left pleural effusion |
| **Pleural Fluid Analysis** | High WBC count, especially lymphocytes |

# Diagnosis

**Pulmonary Tuberculosis (TB)**

### Prescribed Medications

| Medication | Dosage | Duration |
|---|---|---|
| **Myrin P Forte** | 4 tablets/day | 2 months, then Myrin P for 4 more months |
| **Bevidox** | 1 tablet OD (once daily) | As needed |
| **Pantoprazole** | 20 mg OD | As needed (for stomach protection) |
| **Paroxetine** | 25 mg OD | As needed (for mood stabilization) |

---

# 2. Tuberculosis (TB) – Overview

### What is TB?

Tuberculosis is a **bacterial infection** caused by **Mycobacterium tuberculosis**, primarily affecting the **lungs**. However, in immunocompromised individuals, it can **spread to other organs** (extrapulmonary TB).

### Types of TB

1. **Latent TB Infection (LTBI)** – Asymptomatic stage where bacteria remain inactive.
2. **Active TB Infection (ATBI)** – Symptomatic and contagious stage requiring urgent treatment.

### Why is TB Dangerous?

- **Highly infectious**
- **Life-threatening** if untreated
- Requires a **6-month multidrug treatment regimen**

---

# 3. TB Prevalence (Global & Pakistan)

| Statistic | Data |
|---|---|
| **Global Cases (Yearly)** | 9 million develop active TB |
| **Global Deaths (Yearly)** | 2 million die from TB |
| **Affecting Poor Countries** | 95% of cases |
| **Pakistan's TB Rank** | 5th highest worldwide |
| **New TB Cases in Pakistan (Yearly)** | 500,000 |
| **Multidrug-Resistant TB (MDR-TB) Cases (Yearly)** | 15,000 |
| **WHO Eastern Mediterranean TB Burden** | 61% |

### Funding for TB in Pakistan

- **Global Fund** provides major financial support
- **US$ 154 million allocated (2016–2017)**

---

# 4. TB Transmission

### How TB Spreads?

TB is an **airborne disease** that spreads through:
✓ **Coughing** ✓ **Sneezing** ✓ **Speaking**

- **High-Risk Groups:** Household contacts, healthcare workers, and immunocompromised individuals.
- **Most Infectious Cases:** Patients with **AFB-positive sputum** (cavitary disease).
- **AFB-negative cases:** Less contagious but can still spread TB.

---

# 5. Pathogenesis of TB (How TB Affects the Body)

When TB bacteria enter the **lungs**, four possible outcomes occur:

| Stage | Description |
|---|---|
| **1. No Infection** | The immune system fights off the bacteria, and the tuberculin skin test remains negative. |
| **2. Primary TB (Active Disease)** | The bacteria multiply, causing active symptoms. This occurs more in children & immunocompromised individuals. |
| **3. Latent TB (LTBI)** | The immune system controls the infection, preventing symptoms, but the bacteria remain dormant. |
| **4. LTBI → Active TB** | Latent TB can reactivate later due to weak immunity (e.g., in diabetes, HIV, or malnutrition). |

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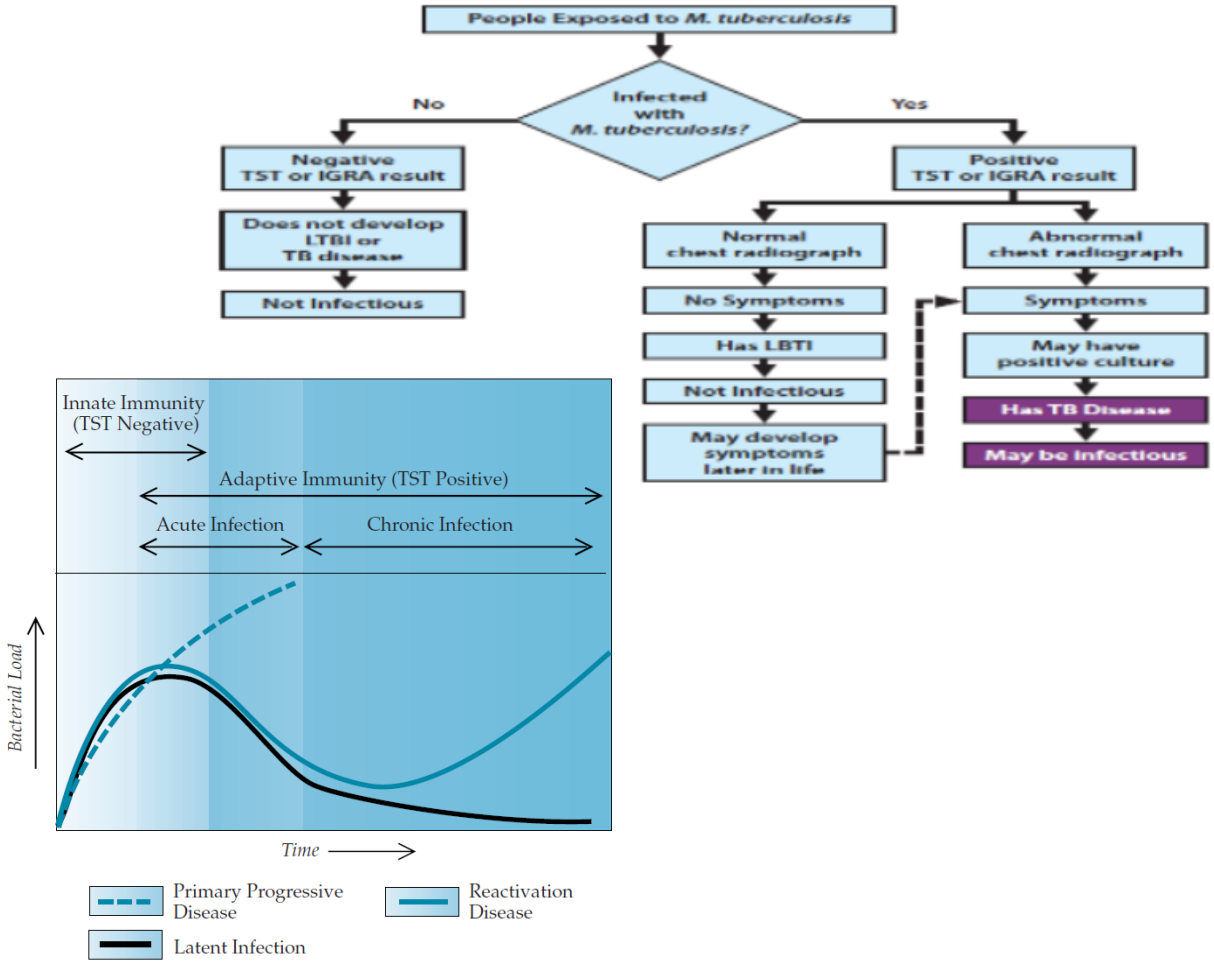

# Classes of TB:

| Class | Type | Description |
|---|---|---|
| **0** | No TB exposure **Not infected** | - No history of TB exposure and no evidence of *M. tuberculosis* infection or disease.<br>- Negative reaction to TST or IGRA. |
| **1** | TB exposure **No evidence of infection** | - History of exposure to *M. tuberculosis*.<br>- Negative reaction to TST or IGRA (given at least 8 to 10 weeks after exposure). |
| **2** | TB infection **No TB disease** | - Positive reaction to TST or IGRA.<br>- Negative bacteriological studies (smear and cultures).<br>- No bacteriological or radiographic evidence of active TB disease. |
| **3** | TB clinically active | - Positive culture for *M. tuberculosis* **OR**<br>- Positive reaction to TST or IGRA, plus clinical, bacteriological, or radiographic evidence of current active TB. |
| **4** | Previous TB disease (**not clinically active**) | - May have past medical history of TB disease.<br>- Abnormal but stable radiographic findings.<br>- Positive reaction to the TST or IGRA.<br>- Negative bacteriologic studies (smear and cultures).<br>- No clinical or radiographic evidence of current active TB disease. |
| **5** | TB suspected | - Signs and symptoms of active TB disease, but medical evaluation **not** complete. |

---

# Forms of TB

## 1. Pulmonary TB (Affects the lungs)

| Type | Description |
|---|---|
| **Primary Pulmonary TB** | - Fever, cough - Atypical pneumonia, pleuritis, pleural effusion<br>- Common in young individuals |
| **Secondary Pulmonary TB** (Reactivation) | - Reactivation of TB bacteria<br>- Symptoms: • Cough, fever • Sweats, anorexia, weight loss, night sweats • General discomfort (malaise) |

## 2. Extrapulmonary TB (Affects organs other than the lungs)

- Can affect lymph nodes, bones, brain, kidneys, intestines
- More common in immunocompromised individuals

---

## Latent TB Infection (LTBI)

| Feature | Description |
|---|---|
| **Symptoms** | Asymptomatic (No symptoms) |
| **Transmission** | Cannot spread TB to others |
| **Sputum Test** | Negative |
| **Chest X-ray** | Normal |
| **Reactivation Risk** | 5% risk of developing active TB |

---

### Signs and Symptoms of Tuberculosis

Tuberculosis (TB) presents with various symptoms, which can be categorized as follows:

#### Common Symptoms:

- Coughing up blood **(Hemoptysis)**
- Fever
- Chest pain
- Chills
- Weight loss
- Night sweats
- Long-term cough
- Loss of appetite
- Fatigu

---

# Diagnosis of Tuberculosis (TB)

| Diagnostic Method | Purpose |
|---|---|
| **1. Physical Examination** | Assess general symptoms (fever, weight loss, cough, night sweats) |
| **2. Chest Radiograph (X-ray)** | Identify lung abnormalities suggestive of TB |
| **3. Microbiology** | Confirm infection through sputum analysis, culture, and PCR tests |

---

## Extrapulmonary Tuberculosis (EPTB) Classification

| Type | Description |
|---|---|
| **1. Tuberculous Pericarditis** | TB infection of the pericardium (heart lining) |
| **2. Tuberculous Lymphadenitis** | TB affecting lymph nodes, commonly in the neck |
| **3. Pleural Tuberculosis** | TB infection in the pleural space (around the lungs) |
| **4. Genitourinary Tuberculosis** | TB affecting the kidneys, bladder, or reproductive organs |
| **5. Musculoskeletal Tuberculosis** | TB of the bones and joints (e.g., spine: Pott’s disease) |
| **6. Abdominal Tuberculosis** | TB infection of the intestines, peritoneum, or abdominal lymph nodes |
| **7. Miliary Tuberculosis** | Widespread TB infection affecting multiple organs, seen as tiny lesions on X-ray |
| **8. Central Nervous System TB** | TB infection in the brain and spinal cord, including TB meningitis |

# Signs & Symptoms of EPTB:

### Symptoms of Tuberculosis

Tuberculosis (TB) manifests in different forms, each presenting with specific and overlapping symptoms:

### Pulmonary TB:

- **Established Pulmonary TB:** Productive cough
- **Primary Pulmonary TB:** Structural abnormalities
- **Tuberculous Pleuritis:** Chest pain

### General Symptoms of Active TB:

- Fever
- Weight loss
- Weakness
- Poor appetite
- Night sweats
- Dry cough

### Specific Forms of TB:

- **Miliary Tuberculosis:** Disseminated TB affecting multiple organs
- **Return of Dormant TB:** Cough with increasing mucus, coughing up blood
- **Extrapulmonary TB:** Common sites include meninges, lymph nodes, bones, joints, and the genitourinary tract
- **Gastrointestinal Symptoms:** Possible in some TB cases

---

# TB Treatment Guidelines

### Goals of Treatment

- Prevent relapse
- Prevent resistance
- Reduce mortality
- Eliminate *Mycobacterium tuberculosis* from the host

---

| Group Name | Category | Anti-TB Drugs |
|---|---|---|
| **GROUP 1** | First-line oral agents | Isoniazid, Rifampicin, Pyrazinamide, Ethambutol, Rifabutin |
| **GROUP 2** | Injectable agents | Streptomycin, Amikacin, Kanamycin, Capreomycin |
| **GROUP 3** | Fluoroquinolones (FQs) | Moxifloxacin, Levofloxacin, Ofloxacin |
| **GROUP 4** | Oral bacteriostatic second-line anti-TB drugs | Ethionamide, Prothionamide, Cycloserine, Para-aminosalicylic acid |
| **GROUP 5** | Drugs with limited data on efficacy and/or long-term safety in the treatment of DR-TB | Bedaquiline, Linezolid, Clofazimine, Amoxicillin/clavulanic acid, Isoniazid (high dose), Thioacetazone, Imipenem/cilastatin, Meropenem |

### Mycobacterium Tuberculosis Subpopulations

| Subpopulation | Characteristics |
|---|---|
| **Rapidly Growing** | - Resides in well-oxygenated cavities - Extracellular |
| **Semidormant (1)** | - Poorly oxygenated - Found in granulomas |
| **Semidormant (2)** | - Both intracellular and extracellular - Small in number |

---

### TB Treatment Options

| Therapy | Duration | Drugs Used |
|---|---|---|
| **Short Therapy** | 6 months | Standard regimen |
| **Long Therapy** | 9 months | Used in special cases |

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## Treatment options for Drug resistance TB

| Pattern of Drug Resistance | Suggested Regimen (Alternative Choice) | Duration of Treatment (months) |
|---|---|---|
| **Isoniazid (± streptomycin)** | Rifampin, pyrazinamide, ethambutol; addition of a fluoroquinolone* may strengthen regimen for patients with extensive disease | 6 |
| **Rifampin** | Isoniazid, ethambutol, and a fluoroquinolone,* plus pyrazinamide for the first 2 months; an injectable agent† may be included for the first 2–3 months for patients with extensive disease | 12–18 |
| **Isoniazid and rifampin (± streptomycin)** | A fluoroquinolone,* pyrazinamide, ethambutol, and an injectable agent,† ± an alternative agent‡ | 18–24 |

---

### Phases of TB Treatment

| Phase | Duration | Drugs Used |
|---|---|---|
| **Intensive Phase** | 2 months | INH, RIF, PZA, EMB (Ethambutol) |
| **Sterilizing Phase** | 4–7 months | INH, RIF, (± EMB) |

### TB and Pregnancy

- Treatment should start as early as possible
- **Recommended regimen:** INH, RIF, EMB for 9 months
- **PZA** (**Pyrazinamide)** may be included
- **Vitamin K** should be added
- **Avoid second-line anti-TB therapy**

# Treatment of EPTB

| Site | Duration of Antimicrobial Therapy (Rating) | Adjunctive Corticosteroids (Rating) |
|---|---|---|
| **Lymph node** | 6 mo (A/I) | Not recommended (D/III) |
| **Bone and joint** | 6–9 mo (A/I) | Not recommended (D/III) |
| **Pleural disease** | 6 mo (A/II) | Not recommended (D/III) |
| **Pericarditis** | 6 mo (A/II) | Strongly recommended (A/I) |
| **CNS, including meningitis** | 9–12 mo (B/II) | Strongly recommended (A/I) |
| **Disseminated disease** | 6 mo (A/II) | Not recommended (D/III) |
| **Genitourinary** | 6 mo (A/II) | Not recommended (D/III) |
| **Peritoneal** | 6 mo (A/II) | Not recommended (D/III) |

# Treatment of Latent TB Infection (LTBI)

| Drug | Duration |
|---|---|
| INH(Isoniazid) | 9 months |
| RIF(Rifampicin) | 4 months |

# Diabetes Mellitus (DM)

*Instructor: Abuzar Khan, PhD*

## Definition:

Diabetes Mellitus (DM) is a **metabolic disorder** affecting the metabolism of **carbohydrates, fats, and proteins**.

**Causes:** DM results from:

- Defects in insulin secretion
- Defects in insulin action (insulin sensitivity)
- Or both

**Characteristics:**

- **Chronic condition**
- **Hyperglycemia (high blood sugar levels)**
- **Impaired insulin secretion** with or without **insulin resistance**

Commonly referred to as DM

## FBS/RBS:

| Category | Fasting Plasma Glucose (FPG/FBS) | 2-Hour Postload Plasma Glucose (OGTT) / RBS | Casual Plasma Glucose |
|---|---|---|---|
| **Normal** | ≤ 100 mg/dL (5.6 mmol/L) | < 140 mg/dL (7.8 mmol/L) | — |
| **Impaired (Pre-diabetes)** | 100–125 mg/dL (5.6–6.9 mmol/L) | 140–199 mg/dL (7.8–11.1 mmol/L) | — |
| **Diabetes Mellitus** | ≥ 126 mg/dL (7.0 mmol/L) | ≥ 200 mg/dL (11.1 mmol/L) | ≥ 200 mg/dL (11.1 mmol/L) + Symptoms |

## Prevalence of Diabetes Mellitus (DM) in Pakistan

**Key Statistics:**

- **26.7%** prevalence rate in Pakistan.
- **Higher in males** than females.
- **More common in urban areas** than rural areas.
- **Pakistan ranks 3rd** in the world for diabetes prevalence.

**Pathophysiology**-The Action of Insulin

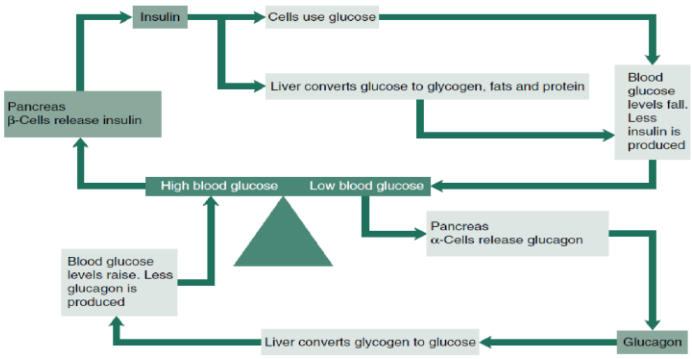
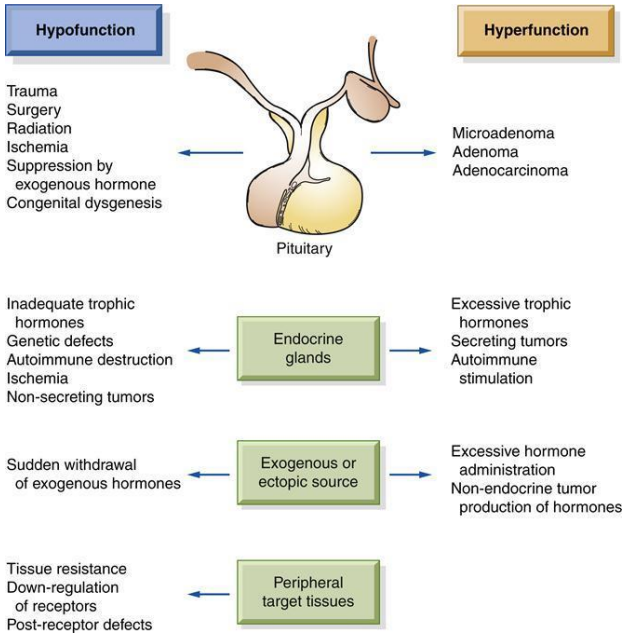



Fig. 45.1 Insulin–glucose relationship detailing the actions of insulin.

**Classification of Endocrine Disorder**




# Classification of Diabetes Mellitus (DM)

1. **Type I Diabetes** – Autoimmune destruction of insulin-producing beta cells, leading to absolute insulin deficiency.
2. **Type II Diabetes** – Insulin resistance with relative insulin deficiency; commonly associated with obesity and lifestyle factors.
3. **Gestational Diabetes (GDM)** – Glucose intolerance diagnosed during pregnancy, which may resolve postpartum or increase the risk of Type II DM later.

## Pathophysiology Type-I DM:

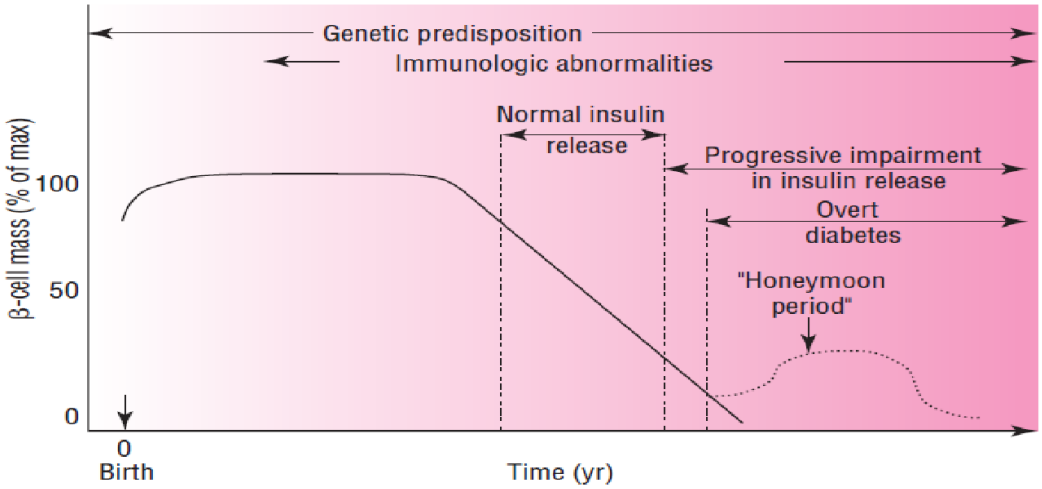
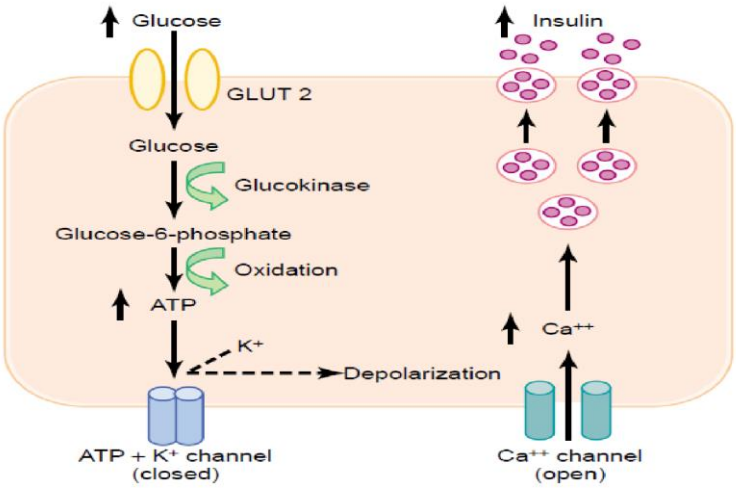
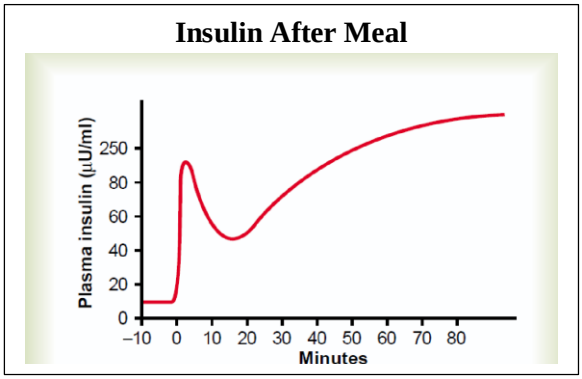


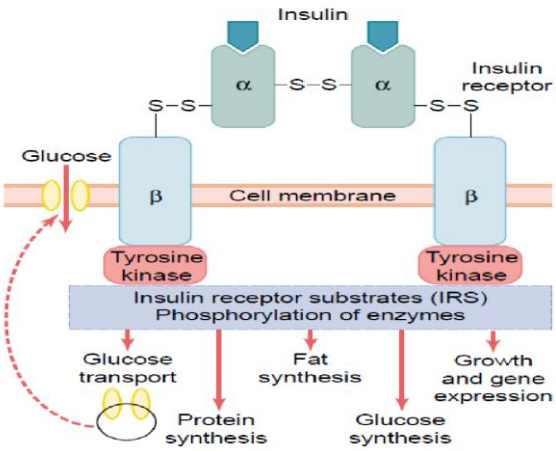

**FIGURE 72–4.** Scheme of the natural history of the β-cell defect in type 1 diabetes mellitus. (From ADA Medical Management of Type of 1 Diabetes, 3rd ed.

**Pathophysiology of Type-II DM of Insulin Release:**




**Pathophysiology Type II DM:**




## Characteristics of Type-II DM:

| Characteristic | Type 1 DM | Type 2 DM |
|---|---|---|
| Age | <30 years[b] | >30 years[b] |
| Onset | Abrupt | Gradual |
| Body habitus | Lean | Obese or history of obesity |
| Insulin resistance | Absent | Present |
| Autoantibodies | Often present | Rarely present |
| Symptoms | Symptomatic[c] | Often asymptomatic |
| Ketones at diagnosis | Present | Absent[d] |
| Need for insulin therapy | Immediate | Years after diagnosis |
| Acute complications | Diabetic ketoacidosis | Hyperosmolar hyperglycemic state |
| Microvascular complications at diagnosis | No | Common |
| Macrovascular complications | Rare | Common |

## Signs and Symptoms of Diabetes Mellitus (DM)

1. **Polyuria** – Excessive urination due to high blood glucose levels causing osmotic diuresis.
2. **Polydipsia** – Increased thirst as a response to dehydration from excessive urination.
3. **Polyphagia** – Excessive hunger due to the inability of glucose to enter cells for energy.

## Other Symptoms:

- Unexplained weight loss (common in Type 1 DM)
- Fatigue and weakness
- Blurred vision
- Slow-healing wounds
- Frequent infections (e.g., skin, urinary tract)

# Complications of Diabetes Mellitus (DM)

Diabetes mellitus leads to multiple complications affecting various organs due to prolonged hyperglycemia. These complications are classified into **macrovascular** and **microvascular** complications.

---

## 1. Macrovascular Complications (Affect Large Blood Vessels)

These complications are due to **atherosclerosis** and **insulin resistance**, leading to an increased risk of cardiovascular diseases.

### Diabetic Cardiomyopathy

- Leading cause of death in diabetic patients.
- Hardening and narrowing of blood vessels (atherosclerosis).
- Increased risk of **hypertension**, **heart failure**, and **silent myocardial infarction (MI)** due to autonomic neuropathy.
- **Coagulation abnormalities** contribute to increased clot formation.

### Hypertension in Diabetes

- Caused by **hyperinsulinemia**, **sympathetic nervous system activation**, and **vascular hypertrophy**.
- Leads to stiffening of blood vessels, causing **elevated blood pressure (BP)**.
- Increases the risk of **heart attacks** and **strokes**.

### Stroke (Cerebrovascular Disease)

- Involves **segmental arteries**, leading to decreased blood supply to the brain.
- **Mismatch between oxygen demand and supply** in brain tissues.
- **Increased blood coagulability** further raises stroke risk.

---

## 2. Microvascular Complications (Affect Small Blood Vessels)

### Diabetic Retinopathy

- **Most common in Type 1 DM**.
- Loss of **capillary pericytes** leads to retinal damage.
- Background retinopathy is the **most common form**.
- Can lead to **vision loss and blindness** if untreated.

### Diabetic Nephropathy (Kidney Damage)

- Chronic hyperglycemia damages **glomerular capillaries**.
- Leads to **proteinuria**, **hypertension**, and eventually **kidney failure**.
- A major cause of **end-stage renal disease (ESRD)**.

---

## 3. Acute Complications of DM

### Diabetic Ketoacidosis (DKA)

- **Occurs mostly in Type 1 DM** due to insulin deficiency.
- Leads to **excessive ketone production**, causing **acidosis**.
- Symptoms: **Fruity breath odor, Kussmaul breathing (deep, rapid respiration), dehydration, and altered mental status**.
- Requires **immediate insulin therapy and fluid replacement**.

### Hyperosmolar Hyperglycemic State (HHS)

- **More common in Type 2 DM**.
- Characterized by **severe dehydration, hyperglycemia (often >600 mg/dL), and hyperosmolarity**.
- **No significant ketone production**.
- Requires **aggressive fluid replacement and insulin therapy**.

## Retinopathy:


# Diabetic Retinopathy Stages

1. **Background Retinopathy**
2. **Pre-Proliferative Retinopathy**
3. **Proliferative Retinopathy**
4. **Maculopathy**

## Diabetic Nephropathy (Microvascular Complication)

- **35-45%** of Type I DM patients are affected.
- Loss of **podocytes** and development of **peritubular fibrosis**.
- **Microalbuminuria**: Excretion of **30 to 300 mg of albumin** per day.
- **Clinical proteinuria**: Excretion of **more than 0.5 g of total protein** per day.
- The **incidence of nephropathy peaks** at approximately **15 to 17 years** and declines somewhat thereafter.
- **Hypertension (HTN)** contributes to progression to **End-Stage Renal Disease (ESRD)**.

---

## Diabetic Neuropathy (Microvascular Complication)

- **Peripheral symmetrical sensorimotor neuropathy**.
- **Numbness or tingling** in the toes and feet.
- **Progressively worsens**.
- **Insensate feet** become vulnerable to trauma, leading to **neuropathic foot ulcers**, which are a frequent cause of **hospitalization and amputation**.
- **Pain**.
- **Cranial neuropathies** causing **diplopia** due to infarction and thrombosis.
- **Amyotrophy** occurs most commonly in **elderly men** with diabetes.
    - Characterized by **severe, unremitting pain and weakness in the thigh muscles**.
    - Associated with **depression, cachexia, and weight loss**.

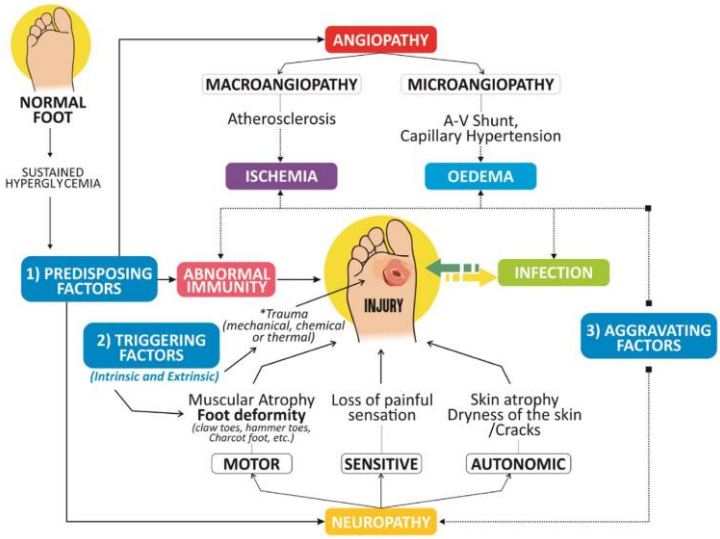
---

## Diabetic Ketoacidosis (DKA)

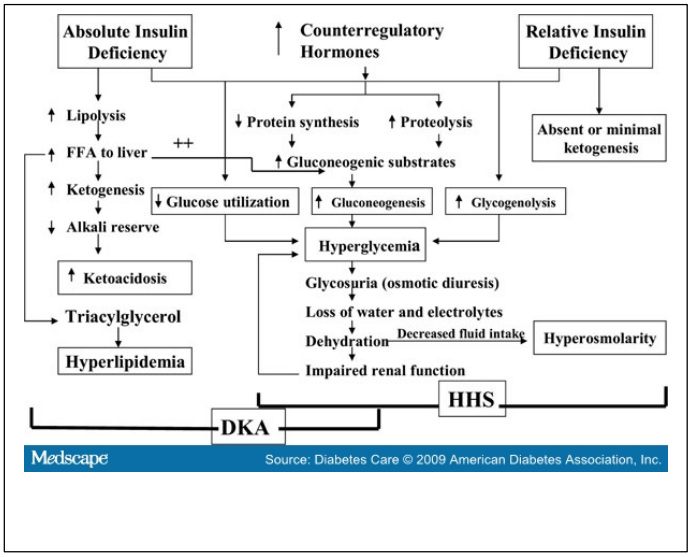
- **Pure insulin deficiency**.
- Occurs in **2% to 5%** of patients with **Type 1 Diabetes Mellitus** per year.
- **Dehydration**.
- **Osmotic diuresis**.
- **Vomiting**.
- **Diarrhea**.

| Test | Average | Range |
|---|---|---|
| **Plasma glucose** | 600 mg/dl (33 mmol/L) | 200–2,000 mg/dl (11–110 mmol/L) |
| **Plasma ketones (positive)** | 1:16 | 1:2–1:64 |
| **Blood betahydroxybutyrate (mmol/L)** | — | 3–25 |
| **Plasma $HCO_3$ (mEq/L)** | 10 | 4–15 |
| **Blood pH** | 7.15 | 6.80–7.30 |
| **$Pco_2$ (mm Hg)** | 20 | 14–30 |
| **Plasma anion gap ($Na^+$ – [Cl + $HCO_3$]) (mEq/L)** | 23 | 16–30 |

## Diabetics Foot Ulcer:




## Hyperosmolar Hyperglycemic State

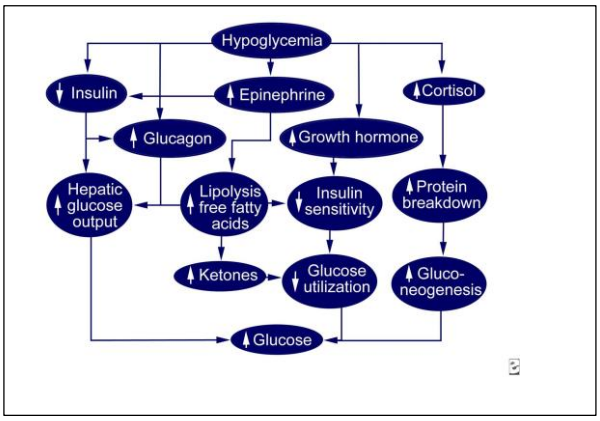



# Somogyi Phenomenon

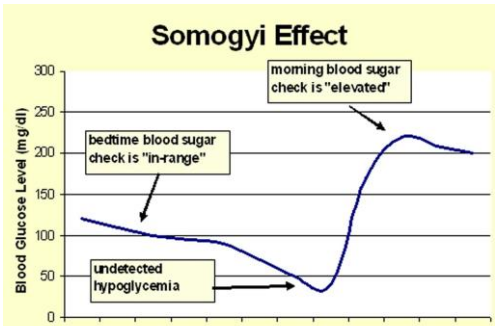
- Described by Dr. Michael Somogyi in the 1930s.
- Occurs when **excess insulin causes nocturnal hypoglycemia**, triggering a **counterregulatory hormone response** (glucagon, cortisol, epinephrine, and growth hormone), which leads to **rebound hyperglycemia in the early morning (4-8 AM)**.
- It is more common in **Type 1 Diabetes Mellitus (DM)**.

## Pathophysiology

1. **Insulin-induced nocturnal hypoglycemia** → Body compensates by releasing:
   - **Glucagon**
   - **Epinephrine**
   - **Cortisol**
   - **Growth hormone**
2. This leads to **early morning hyperglycemia**.




Somogyi Lab Findings




## Patient History

- Morning hyperglycemia (4-8 AM)
- Unnoticed nocturnal hypoglycemia
- Post-hypoglycemic hyperglycemia
- Hypoinsulinemia

## Lab Findings

- **Fasting blood glucose**
- **Nocturnal blood glucose monitoring** (detects nighttime hypoglycemia)
- **Hemoglobin A1C (Hgb A1C)**
- **Frequent glucose sampling**

## Key Point:

The Somogyi phenomenon is often mistaken for **insufficient insulin**, leading to unnecessary **insulin dose increases**, which worsen the problem. **Monitoring nocturnal glucose levels** helps in proper diagnosis and management.

# Dawn Phenomenon

The **Dawn Phenomenon (Dawn Effect)** is an **early-morning rise in blood glucose levels** occurring between **2 AM and 8 AM**. It is seen in both **Type 1 and Type 2 Diabetes Mellitus (DM)** and results from **hormonal changes** that reduce insulin sensitivity.

### Causes & Mechanism

1. **Type 1 DM (T1D) → Nocturnal growth hormone spikes** reduce insulin effectiveness.
2. **Type 2 DM (T2D) → Increased hepatic glucose production** (glycogenolysis & gluconeogenesis) without enough insulin response.

## Diagnosis

- **Blood Glucose (BG) test at 3-5 AM**
- **Nocturnal BG monitoring** to differentiate from the **Somogyi phenomenon**
- **Continuous Glucose Monitoring System (CGMS)** for precise tracking

## Key Point:

Unlike the **Somogyi Phenomenon**, which results from **nocturnal hypoglycemia and a rebound effect**, the **Dawn Phenomenon** is a **natural hormonal rise causing fasting hyperglycemia**. Proper **insulin adjustment and meal planning** help manage this condition.

| Feature comparing | The dawn phenomenon | The Somogyi effect |
|---|---|---|
| Definition | Recurring early morning hyperglycaemia | Early morning hyperglycaemia due to treatment with excessive amount of exogenous insulin |
| Cause | Decrease of insulin secretion between 3a.m. and 5a.m. and increase of insulin-antagonistic hormones | Nocturnal hypoglycemia due to excessive dose of insulin and the next early morning hyperglycemia due to increase of insulin-antagonistic hormones |
| Occurrence | Type 1 diabetic patients<br>Type 2 diabetic patients with no insulin therapy | Type 1 diabetic patients<br>Type 2 diabetic patients with insulin therapy |
| Incidence | Type 1 diabetic children — 27.4%<br>Type 1 diabetic adults — 24.1%<br>Type 2 diabetic adults — 3%<br>Type 1 diabetes generally — 54%<br>Type 2 diabetes generally — 55% | Type 1 and 2 diabetic patients — 12.6–67%<br>Type 1 diabetic patients — 18% |
| Diagnosis | Measurement of the plasma glucose concentration between 3 a.m. and 5 a.m. during next several nights<br>CGMS<br>The confirmative result: high/normal plasma glucose level | Measurement of the plasma glucose concentration between 3 a.m. and 5 a.m. during next several nights<br>CGMS<br>The confirmative result: low plasma glucose level |

# Treatment of Diabetes: (HBA1C To Plasma Blood Glucose)

Table 6.1—Mean glucose levels for specified A1C levels (37,43)

| A1C | Mean plasma glucose* | | Mean fasting glucose | | Mean premeal glucose | | Mean postmeal glucose | | Mean bedtime glucose | |
|---|---|---|---|---|---|---|---|---|---|---|
| % (mmol/mol) | mg/dL | mmol/L | mg/dL | mmol/L | mg/dL | mmol/L | mg/dL | mmol/L | mg/dL | mmol/L |
| 6 (42) | 126 (100–152) | 7.0 (5.5–8.5) | | | | | | | | |
| 5.5–6.49 (37–47) | | | 122 (117–127) | 6.8 (6.5–7.0) | 118 (115–121) | 6.5 (6.4–6.7) | 144 (139–148) | 8.0 (7.7–8.2) | 136 (131–141) | 7.5 (7.3–7.8) |
| 6.5–6.99 (47–53) | | | 142 (135–150) | 7.9 (7.5–8.3) | 139 (134–144) | 7.7 (7.4–8.0) | 164 (159–169) | 9.1 (8.8–9.4) | 153 (145–161) | 8.5 (8.0–8.9) |
| 7 (53) | 154 (123–185) | 8.6 (6.8–10.3) | | | | | | | | |
| 7.0–7.49 (53–58) | | | 152 (143–162) | 8.4 (7.9–9.0) | 152 (147–157) | 8.4 (8.2–8.7) | 176 (170–183) | 9.8 (9.4–10.2) | 177 (166–188) | 9.8 (9.2–10.4) |
| 7.5–7.99 (58–64) | | | 167 (157–177) | 9.3 (8.7–9.8) | 155 (148–161) | 8.6 (8.2–8.9) | 189 (180–197) | 10.5 (10.0–10.9) | 175 (163–188) | 9.7 (9.0–10.4) |
| 8 (64) | 183 (147–217) | 10.2 (8.1–12.1) | | | | | | | | |
| 8.0–8.5 (64–69) | | | 178 (164–192) | 9.9 (9.1–10.7) | 179 (167–191) | 9.9 (9.3–10.6) | 206 (195–217) | 11.4 (10.8–12.0) | 222 (197–248) | 12.3 (10.9–13.8) |
| 9 (75) | 212 (170–249) | 11.8 (9.4–13.9) | | | | | | | | |
| 10 (86) | 240 (193–282) | 13.4 (10.7–15.7) | | | | | | | | |
| 11 (97) | 269 (217–314) | 14.9 (12.0–17.5) | | | | | | | | |
| 12 (108) | 298 (240–347) | 16.5 (13.3–19.3) | | | | | | | | |

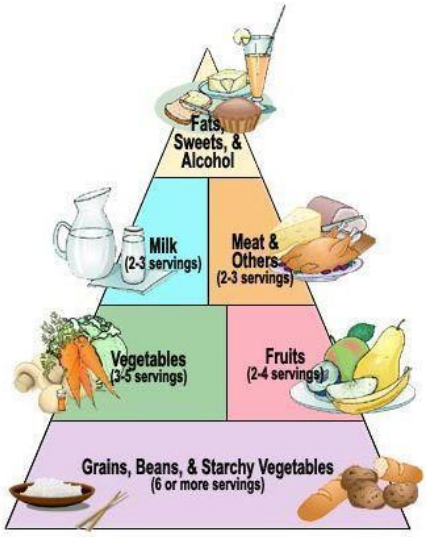
## Goals of Treatment

1. **Reduce the risk of complications** – both **microvascular (retinopathy, nephropathy, neuropathy)** and **macrovascular (stroke, heart disease).**
2. **Control symptoms** – such as excessive thirst, urination, and fatigue.
3. **Reduce mortality** – by preventing severe complications.
4. **Improve quality of life** – through better glucose control and lifestyle management.

## General Approach to Treatment

1. **Set Target Levels:**
   - Blood glucose, **HbA1C <7%**, blood pressure, and lipid levels.
2. **Lifestyle Modifications:**
   - **Dietary changes** – balanced intake of carbs, proteins, and fats.
   - **Exercise** – regular physical activity to improve insulin sensitivity.
3. **Medications:**
   - **Oral Hypoglycemic Therapy** for **Type 2 DM**.
   - **Insulin therapy** for **Type 1 DM** and severe cases of **Type 2 DM**.
4. **Self-Monitoring of Blood Glucose (SMBG):**
   - Regular glucose testing to ensure stable levels.
5. **Lab Assessments:**
   - Routine **HbA1C, lipid profile, kidney function, and eye exams** to prevent complications.

### Non-Pharmacological Management:




Treatment Option for overweight and obesity in Type-2 Diabetes

Table 7.1–Treatment options for overweight and obesity in type 2 diabetes

| | BMI category (kg/m²) | | | | |
|---|---|---|---|---|---|
| Treatment | 25.0–26.9 (or 23.0–26.9*) | 27.0–29.9 | 30.0–34.9 (or 27.5–32.4*) | 35.0–39.9 (or 32.5–37.4*) | ≥40 (or ≥37.5*) |
| Diet, physical activity, and behavioral therapy | † | † | † | † | † |
| Pharmacotherapy | | † | † | † | † |
| Metabolic surgery | | | † | † | † |

*Cutoff points for Asian American individuals. †Treatment may be indicated for selected motivated patients.

# Pharmacotherapy

## HbA1C Levels and Treatment Approach

- **7-8% HbA1C** → Start with **monotherapy**.
- **More than 8% HbA1C** → Start with **two-drug therapy**.
- **Obese patients → Biguanides** as the **first-line** treatment.
- **Normal or lean patients → Sulfonylureas (SU)** as the **first-line** treatment.
- **If HbA1C > 9% → Combination of Biguanides + SU** is recommended.
- **Biguanides + SU** is the most **cost-effective** combination.

## Pharmacotherapy Options

### 1. Biguanides

| Drug | Benefits | Considerations |
|---|---|---|
| **Metformin** | - Reduces HbA1C by **1.5-2%**.<br>- Reduces **LDL cholesterol**.<br>- Reduces **weight**.<br>- Improves **macrovascular complications** (UKPDS study). | - First-line choice **in** T2DM**.**<br>- Preferred for obese diabetic patients**.** |

### 2. Sulfonylureas (SU)

| Drug | Benefits | Considerations |
|---|---|---|
| **Sulfonylureas** | - Reduces HbA1C by **1-2%**.<br>- Reduces **microvascular and macrovascular complications**. | - **Start with a low dose**, gradually increase.<br>- **Divide dose into BD** or use **SR formulation**.<br>- **Effective in new diabetics (up to 5 years)**.<br>- **Effective in normal or modestly obese patients**.<br>- **Short-acting SU** preferred in patients at **risk of hypoglycemia**. |

### 3. Short-Acting Insulin Secretagogues (Meglitinides)

| Drug | Benefits | Considerations |
|---|---|---|
| **Meglitinides** | - **Short half-life**.<br>- **Low risk of hypoglycemia**.<br>- Reduces **HbA1C by 0.5-1%**.<br>- **Rapid action**.<br>- Effectively reduces **postprandial plasma glucose**. | - **Effective as monotherapy**. |

| Drug | Benefits | Considerations |
|---|---|---|
| | - Reduces **glucose toxicity**. | |

### 4. α-Glucosidase Inhibitors

| Drug | Benefits | Considerations |
|---|---|---|
| **α-Glucosidase Inhibitors** | - **Effective only in postprandial hyperglycemia**.<br>- Reduces HbA1C by **0.8%**.<br>- **Low risk of hypoglycemia**. | - **Must be taken before meals**. |

### 5. Thiazolidinediones (TZDs)

| Drug | Benefits | Considerations |
|---|---|---|
| **TZDs** | - Reduces HbA1C by **1.5%**.<br>- **Reduces insulin resistance** in muscle, fat, and liver.<br>- Decreases **serum triglyceride levels**.<br>- **Increases HDL**, but also increases **LDL**.<br>- Shows **cardioprotection and beta-cell protection**. | - **May not be suitable for patients with heart failure**. |

### 6. Glucagon-Like Peptide-1 (GLP-1) Agonists

| Drug | Benefits | Considerations |
|---|---|---|
| **Semaglutide (GLP-1 Agonists)** | - **Glucose-dependent insulin release**.<br>- **Slows gastric emptying**.<br>- **Inhibits inappropriate glucagon release**.<br>- **Lower risk of hypoglycemia**.<br>- Reduces HbA1C by **1-1.6%**. | - **Useful for patients with high postprandial glucose**. |

### 7. Dipeptidyl Peptidase-IV (DPP-4) Inhibitors

| Drug | Benefits | Considerations |
|---|---|---|
| **Sitagliptin (DPP-4 Inhibitors)** | - **Incretin-based therapy**.<br>- **Low risk of hypoglycemia**.<br>- DPP-4 **degrades active peptides**, including **GLP-1**. | - **May be combined with other antidiabetic agents**. |

## 8. Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors

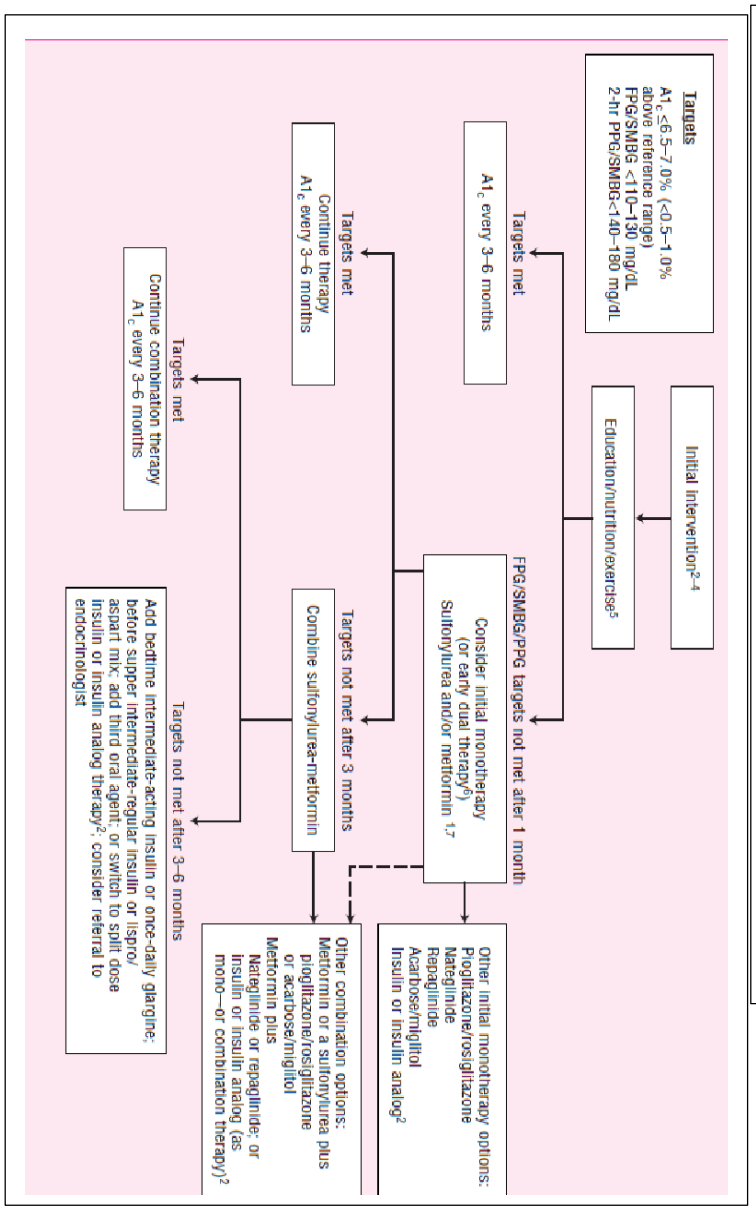
| Drug | Benefits | Considerations |
|---|---|---|
| **Dapagliflozin, Empagliflozin (SGLT2 Inhibitors)** | - Promotes **glucose excretion through urine**.<br>**- Lowers blood glucose levels**.<br>**- Weight loss benefit**.<br>**- Cardiovascular protection**. | **- Monitor kidney function**. - **Risk of dehydration and UTI**. |

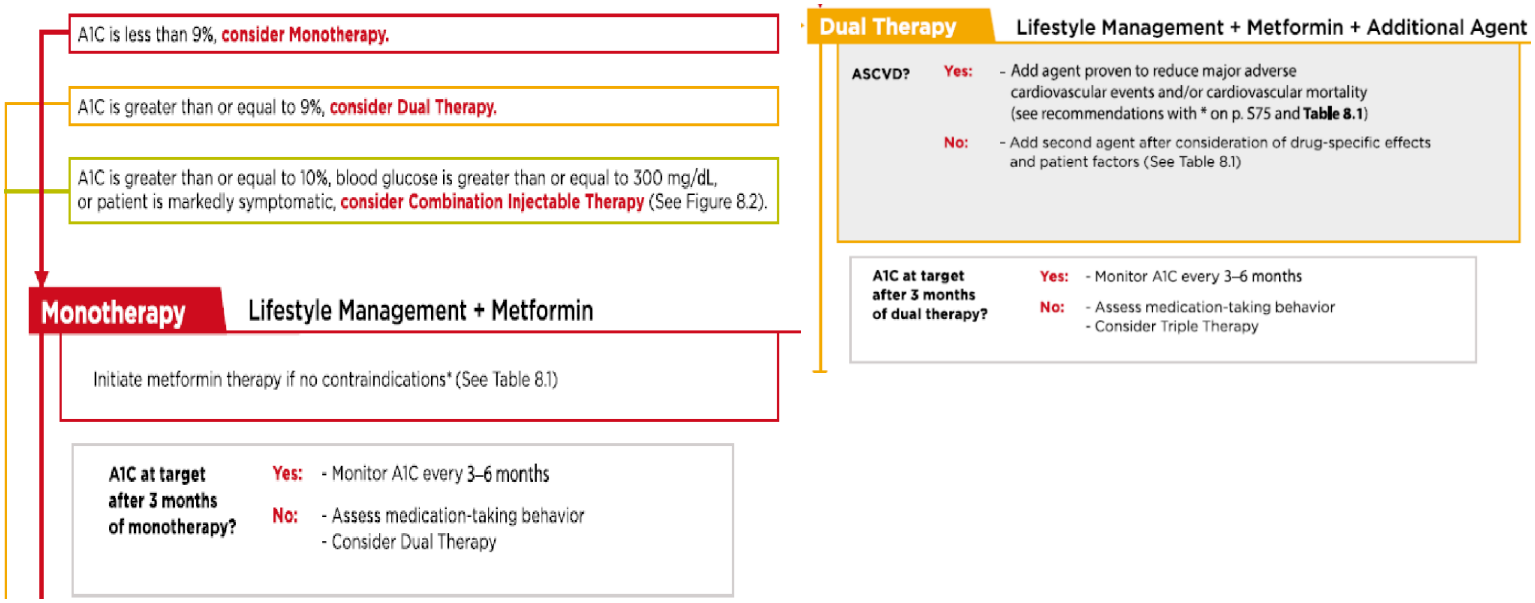
## Summary of Antidiabetic Drug Classes

| Drug Class | Examples | Mechanism of Action | HbA1C Reduction | Key Benefits | Considerations |
|---|---|---|---|---|---|
| **Biguanides** | Metformin | Decreases hepatic glucose production & improves insulin sensitivity | **1.5-2%** | Weight loss, LDL reduction, improves macro vascular complications | First-line for **T2DM**, avoid in renal impairment |
| **Sulfonylureas (SU)** | Glimepiride, Glipizide | Stimulates pancreatic insulin secretion | **1-2%** | Effective in early diabetes, reduces microvascular complications | Risk of **hypoglycemia**, weight gain |
| **Meglitinides** | Repaglinide, Nateglinide | Short-acting insulin secretagogue | **0.5-1%** | Rapid action, reduces postprandial glucose | Short half-life, **low risk of hypoglycemia** |
| **α-Glucosidase Inhibitors** | Acarbose, Miglitol | Inhibits carbohydrate digestion & absorption | **0.8%** | Effective in **postprandial hyperglycemia** | Take before meals, **low hypoglycemia risk** |
| **Thiazolidinediones (TZDs)** | Pioglitazone, Rosiglitazone | Reduces insulin resistance at muscle, fat, and liver | **1.5%** | Improves lipid profile, beta-cell protection | Increases **HDL & LDL**, **cardioprotective** |
| **GLP-1 Agonists** | Semaglutide, Exenatide | Enhances insulin secretion, slows gastric emptying | **1-1.6%** | Low hypoglycemia risk, weight loss | Injectable, useful for **postprandial glucose control** |
| **DPP-4 Inhibitors** | Sitagliptin, Vildagliptin | Inhibits DPP-4 enzyme to prolong incretin action | **0.5-1%** | Low hypoglycemia risk | Safe in renal impairment |
| **SGLT2 Inhibitors** | Dapagliflozin, Empagliflozin | Inhibits glucose reabsorption in kidneys | **0.5-1%** | Weight loss, CV benefits, lowers BP | Risk of **UTI & dehydration**, avoid in renal failure |

**TABLE 72–13. Add-On Dual Therapy: Average $HbA_{1c}$ Reductions[a]**

| Drug Combination | Change in $HbA_{1c}$ (%) | Number of Studies | Number of Subjects |
|---|---|---|---|
| Sulfonylurea + metformin | −2.2 | 8 | 458 |
| Sulfonylurea + insulin | −1.9 | 17 | 88 |
| Meglitinide + thiazolidinedione | −1.7 | 1 | 434 |
| Metformin + insulin | −1.7 | 8 | 138 |
| Sulfonylurea + α-glucosidase inhibitor | −1.6 | 3 | 177 |
| Metformin + meglitinide | −1.4 | 3 | 226 |
| Insulin + α-glucosidase inhibitor | −1.2 | 1 | 20 |
| Insulin + thiazolidinedione | −1.2 | 7 | 850 |
| Sulfonylurea + thiazolidinedione | −1.1 | 12 | 1315 |
| Metformin + thiazolidinedione | −0.9 | 3 | 284 |
| Metformin + α-glucosidase inhibitor | −0.4 | 3 | 173 |



**Triple Therapy** Lifestyle Management + Metformin + Two Additional Agents

Add third agent based on drug-specific effects and patient factors[#] (See Table 8.1)

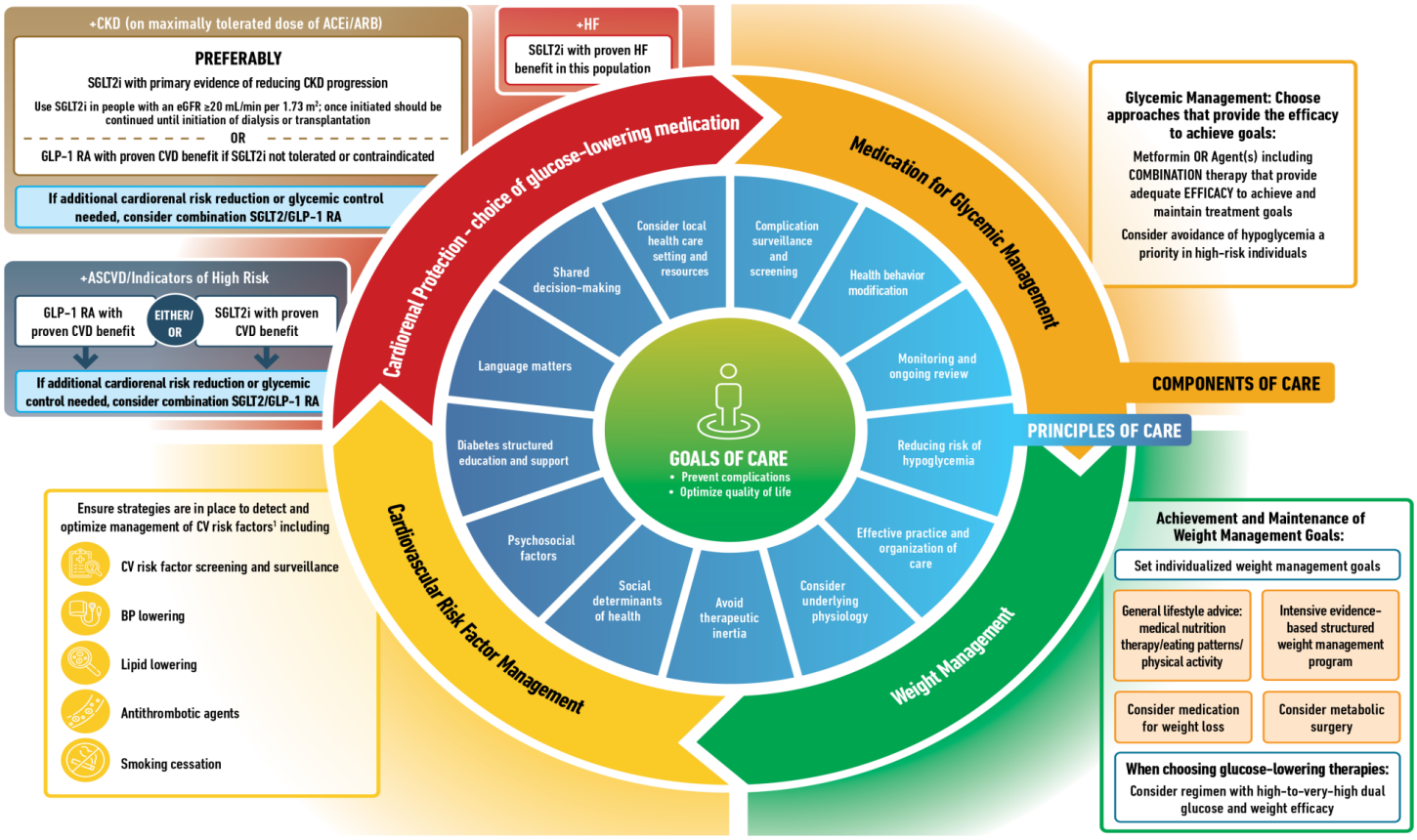
**A1C at target after 3 months of triple therapy?**

**Yes:** - Monitor A1C every 3–6 months

**No:** - Assess medication-taking behavior
- Consider Combination Injectable Therapy (See Figure 8.2)

**Combination Injectable Therapy** (See Figure 8.2)

## HOLISTIC PERSON-CENTERED APPROACH TO T2DM MANAGEMENT



# TREATMENT OF DIABETES

**Insulin Therapy**

## Insulin Preparations - Which One to Use?

| Type of Insulin | Usage |
|---|---|
| **Rapid-acting insulin** | To the meal with the highest preprandial BGL |
| **Intermediate-acting insulin** | In the morning or night |
| **Insulin premixed** | For ease of use |
| **Basal insulin** | To reduce both postprandial and fasting BGLs |

---

## Insulin Dose

**Fixed-Dose Insulin**

- Carbohydrate to Insulin Ratio
- Sliding-Scale Insulin Therapy (SSI)
- Insulin dose calculation and division based on weight, age, and glycemia

---

## Insulin Timing

**Timing depends on blood glucose profile:**

- If **fasting BGL is high**, give at bedtime
- If **fasting BGL on target but evening BGL high**, give in the morning
- If **both fasting and evening BGLs are high**, give **bd NPH or once daily glargine**

---

## Insulin Dose

| Dosage Calculation | Details |
|---|---|
| **Total Insulin Dose** | 0.5-1 Unit/kg |
| **Basal-Bolus Division** | 50% basal and 50% mealtime |
| **Correction Dose** | 1-2 extra units for each 50 gm of glucose |

## Conventional Therapy

| Meal | Dose Ratio |
|---|---|
| **Breakfast** | 2/3 or 3/4 of total daily dose |
| **Dinner** | Remaining dose |

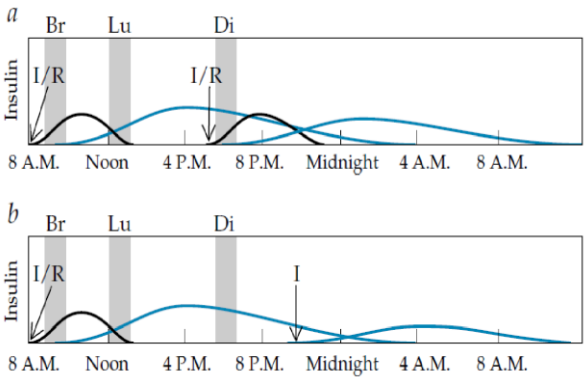
## Ratio of Insulin to Rapid-Acting (I:R) Before Meals

| Meal | Ratio |
|---|---|
| **Before Breakfast** | 2:1 or 4:2 |
| **Before Supper** | 1:1 |

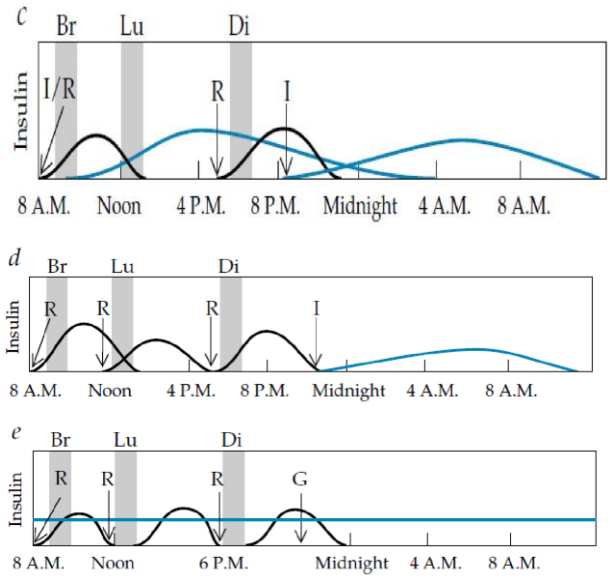
**Insulin dose is usually divided so that:**

- **One-half is administered before breakfast**
- **One-fourth before dinner**
- **One-fourth at bedtime**

**Conventional Insulin Therapy:**




**Intensive Insulin Therapy:**




## Regular Insulin Sliding Scale

| Blood sugar (mg/dl) | Low dose scale | Mod dose scale | High dose scale |
|---|---|---|---|
| <70 | Initiate hypoglycemia protocol | | |
| 70-130 | 0 | 0 | 0 |
| 131-180 | 2 | 4 | 8 |
| 181-240 | 4 | 8 | 12 |
| 241-300 | 6 | 10 | 16 |
| 301-50 | 8 | 12 | 20 |
| 351-400 | 10 | 16 | 24 |
| >400 | 12 | 20 | 28 |

# Hyperthyroidism

### Introduction

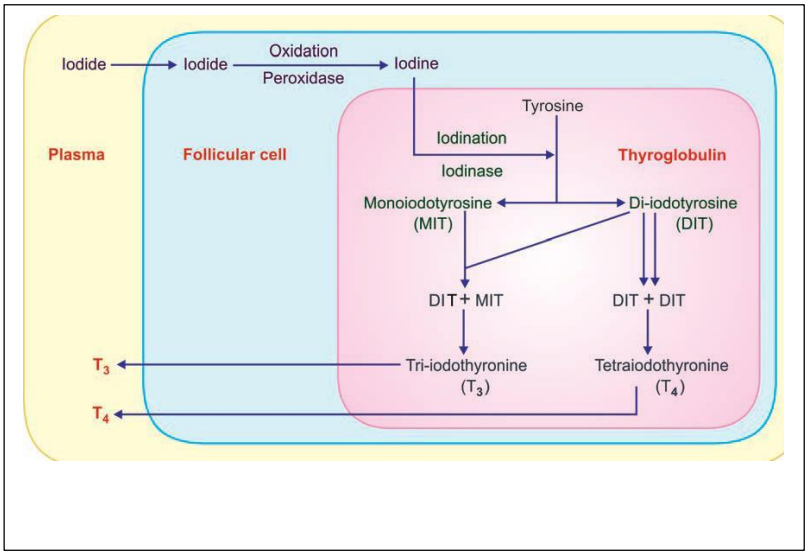
Hyperthyroidism refers to a group of disorders characterized by:

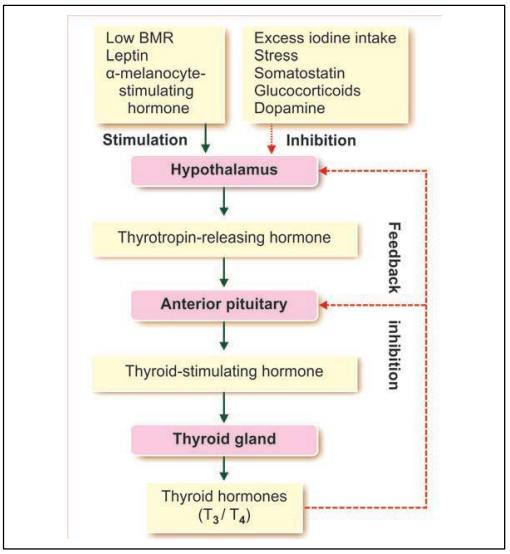
- Excess **synthesis and secretion** of thyroid hormones.
- Overactivity of the **thyroid gland**, leading to a condition called **thyrotoxicosis** (a hypermetabolic state caused by high thyroid hormone levels).

### Key Terms

- **Hyperthyroidism:** The excessive production of thyroid hormones by the thyroid gland.
- **Thyrotoxicosis:** A condition resulting from excess thyroid hormones in the bloodstream, leading to increased metabolism.

## Physiology of Thyroid Hormones:




## Physiology of Thyroid Hormones

### Thyroid Hormone Composition

- **93% T4 (Thyroxine) and 7% T3 (Triiodothyronine)**
- **T4 converts to T3** in the body (T3 is the active form).
- **T3 is four times more active** than T4.

---

## Functions of Thyroid Hormones

1. **Basal Metabolic Rate (BMR)**
    - Increases BMR, leading to higher energy consumption.

2. **Protein Metabolism**
    - Stimulates **DNA transcription** and **RNA translation**.
    - Increases **mitochondrial activity** and **cellular enzyme function**.
    - Enhances **protein synthesis** and **protein breakdown**.
3. **Carbohydrate Metabolism**
    - Increases **glucose absorption and synthesis**.
    - Promotes **glucose uptake** into cells.
    - Stimulates **glycogen breakdown (glycogenolysis)**.
4. **Fat Metabolism**
    - **Mobilizes fats** and increases **fatty acid levels** in the blood.
5. **Body Temperature**
    - Enhances **thermogenesis (heat production)**.
6. **Growth and Development**
    - Essential for **fetal growth** and overall body development.
7. **Body Weight**
    - Regulates metabolism, affecting weight gain or loss.
8. **Cardiovascular System (CVS)**
    - Influences **heart rate (HR), force of contraction (FC), blood pressure (BP)**, and **red blood cell production (erythropoiesis)**.
9. **Gastrointestinal System (GIT)**
    - Increases **peristalsis** (movement of food through the intestines).
    - Boosts **appetite**.
10. **Respiratory System:** Increases **rate and depth** of breathing.

11. **Central Nervous System (CNS)**

    - Essential for **brain development** and maintaining an **active mind**.
    - **Excess T3/T4 (Hyperthyroidism):** Causes **nervousness, paranoia, anxiety**.
    - **Deficiency (Hypothyroidism):** Leads to **lethargy and somnolence (excessive sleepiness)**.

12. **Sleep**: Regulated by thyroid hormones (imbalance can cause sleep disturbances).

13. **Sexual System**: Affects reproductive health and function.

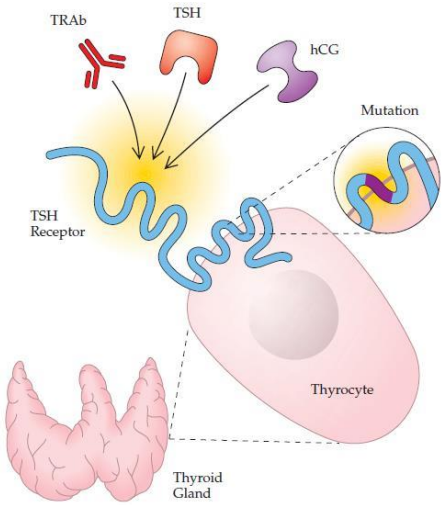
14. **Muscles**: Can cause **thyrotoxic myopathy** (muscle weakness in hyperthyroidism).

---

## Etiological Classification of Thyrotoxicosis:

| Cause | Individual Diseases |
|---|---|
| **Abnormal stimulation of the thyroid gland** | Graves disease, hCG-mediated thyrotoxicosis, TSH-mediated thyrotoxicosis |
| **Thyroid gland autonomy** | Toxic adenoma, Toxic multinodular goiter, Congenital thyrotoxicosis, Iodine-induced hyperthyroidism, Thyroid cancer–related thyrotoxicosis |

| Cause | Individual Diseases |
|---|---|
| **Gland inflammation with unregulated thyroid hormone release** | Subacute (de Quervain) thyroiditis, Lymphocytic thyroiditis, Amiodarone-induced thyrotoxicosis (type 2), Acute thyroiditis |




## 1. Abnormal stimulation of the thyroid gland:

The **thyroid gland** is activated by **TSH (a thyroid-controlling hormone), hCG (a pregnancy-related hormone), and TRAb (immune proteins that can overstimulate the thyroid)**. These signals act on **thyrocytes (thyroid cells)** to produce hormones. A **mutation (gene change)** can also make the thyroid overactive, leading to **Graves' disease (a condition that causes too much thyroid hormone and increases body activity).**

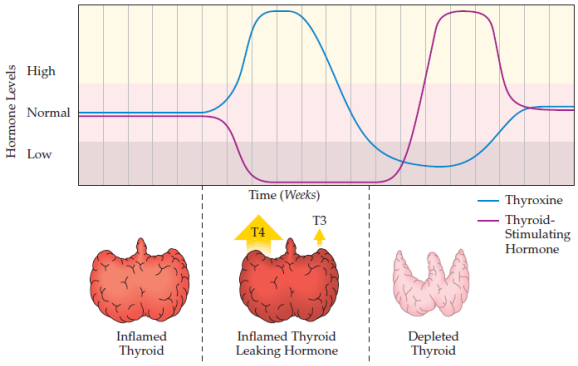
---

## 2. Thyroid Gland Autonomy

- **Increased production of thyroid hormones** without regulation by **TSH (Thyroid-Stimulating Hormone)**.
- Caused by **hyperplastic** (excessive cell growth) and **neoplastic** (tumor-related) conditions.
- Includes **solitary or multiple thyroid adenomas** (benign tumors of the thyroid).
- **TSH levels decrease** due to excessive hormone production.
- **Genetic and environmental factors** contribute to the development of autonomous thyroid function.
- **Iodine intake** may influence thyroid autonomy.

---

## 3. Glandular Inflammation (Thyroiditis)




- **Causes of thyroid gland inflammation:**
  - **Infectious diseases** (bacterial or viral infections).
  - **Autoimmune conditions** (e.g., Hashimoto's thyroiditis, Graves' disease).
  - **Pharmacologic toxicity** (damage caused by certain medications).
- **Effects of inflammation:**
  - **Thyrocyte death** (destruction of thyroid cells).
  - **Disruption of follicular architecture** (damage to thyroid tissue structure).
  - **Unregulated leakage of thyroid hormones** into the bloodstream, leading to **thyrotoxicosis** (excess thyroid hormone levels).

---

## Physical Examination of Hyperthyroidism

- **Behavioral Signs:** Anxious, hyperactive.
- **Speech & Cardiovascular Signs:**
  - Pressured speech.
  - **Tachycardia** (rapid heartbeat).
  - **Systolic hypertension** (high upper blood pressure reading).
  - **Widened pulse pressure** (large difference between systolic and diastolic pressure).
- **Skin & Hair Changes:**
  - Velvety, warm, and moist skin.
  - Oily hair.
- **Eye Signs:**
  - Staring gaze.
  - **Lid lag** (upper eyelid moves slowly when looking downward).
- **Heart & Muscle Involvement:**
  - **Prominent systolic flow murmur** (heart murmur due to increased blood flow).
  - **Proximal leg muscle weakness** and **tremors**.

---

## Clinical Presentation of Hyperthyroidism

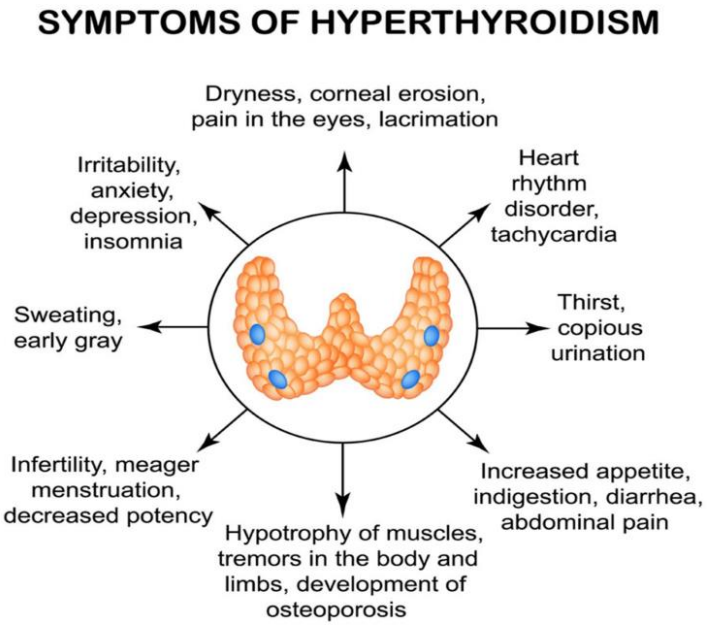
- **Unexplained Weight Loss** despite a good appetite.
- **Heat Intolerance** (feeling excessively warm).
- **Tremors** (shakiness in hands or body).
- **Palpitations & Anxiety** (rapid heartbeat and restlessness).
- **Fatigue & Insomnia** (tiredness but difficulty sleeping).
- **Dyspnea** (shortness of breath).
- **Atypical Chest Pain** (discomfort not linked to typical heart conditions).

---

## Symptoms of Hyperthyroidism

### Common Symptoms:

- **Eyes:** Dryness, eye pain, corneal erosion, excessive tearing.
- **Heart:** Rapid heartbeat, irregular heart rhythm.
- **Metabolism:** Increased thirst, frequent urination, excessive hunger, digestion issues, diarrhea, and abdominal pain.
- **Nervous System:** Irritability, anxiety, depression, insomnia.
- **Muscles & Bones:** Weak muscles, body tremors, osteoporosis (bone loss).



- **Reproductive Health:** Irregular or light menstruation, infertility, reduced sexual function.
- **Skin & Hair:** Excessive sweating, early graying of hair.

These symptoms can vary in severity and may require medical attention to manage thyroid hormone levels effectively.

---

## Thyroid Storm

**Definition:**

- A **life-threatening** medical emergency caused by **severe thyrotoxicosis** (excess thyroid hormones).

**Clinical Features:**

- **High fever** (often >103°F).
- **Tachycardia** (rapid heart rate).
- **Tachypnea** (rapid breathing).
- **Dehydration** (due to excessive sweating and fluid loss).
- **Neurological symptoms:** Delirium, confusion, or coma.
- **Gastrointestinal symptoms:** Nausea, vomiting, and diarrhea.

**Possible Precipitating Factors:**

- Infection, surgery, trauma, stress, or sudden withdrawal of thyroid medication.

---

## Diagnosis of Thyroid Storm

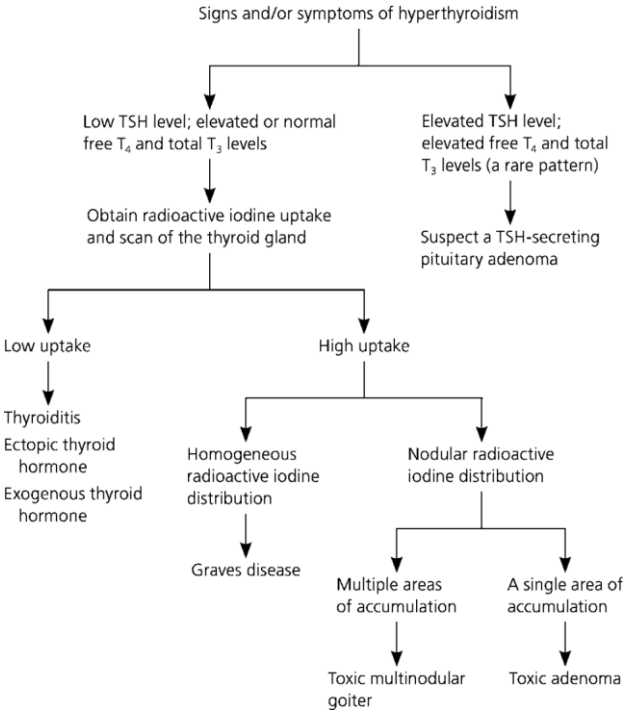
1. **Physical Examination:**
    - High fever, rapid heartbeat, and signs of severe hyperthyroidism.
2. **Thyroid Function Tests (TFTs):**
    - **Elevated T3 & T4** (thyroid hormones).
    - **Suppressed TSH** (very low thyroid-stimulating hormone).
3. **Thyroid Scan:**
    - Determines if the thyroid is overactive.
4. **Thyroid Biopsy:**
    - Helps diagnose underlying thyroid disorders if needed.

---

## Differential Diagnosis of Hyperthyroidism

### Simplified Flowchart for Diagnosing Hyperthyroidism

1. **Step 1: Check TSH, T4, and T3 Levels**
   - **Low TSH + High/Normal T4 & T3** → Do a radioactive iodine scan.
   - **High TSH + High T4 & T3** → May indicate a rare **TSH-secreting tumor** in the pituitary gland.
2. **Step 2: Analyze Radioactive Iodine Uptake**
   - **Low Uptake:** Could be due to **thyroiditis, ectopic thyroid hormone, or external thyroid medication.**
   - **High Uptake:**
     - **Even (homogeneous) distribution** → Likely **Graves' disease.**
     - **Uneven (nodular) distribution:**
       - Multiple areas of iodine accumulation → Toxic multinodular goiter.
       - Single area of iodine accumulation → Toxic adenoma**.**

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# Management of Hyperthyroidism

### Goal of Therapy

- **Eliminate excess thyroid hormones.**
- **Minimize symptoms** and prevent long-term complications.
- Treatment is **individualized** based on:
  - **Type and severity** of hyperthyroidism.
  - **Patient's age and gender.**
  - **Other existing conditions.**
  - **Response to previous treatments.**

---

### Treatment Options for Hyperthyroidism

| Treatment | Description |
|---|---|
| **1. Anti-Thyroid Medications** | Medications to suppress thyroid hormone production. |
| **2. Radioactive Iodine (RAI)** | Destroys thyroid tissue to reduce hormone production. |
| **3. Surgery** | Partial or complete thyroid removal. |

---

## 1. Anti-Thyroid Drugs (ATDs)

### When to Consider ATDs?

- **Temporary treatment** for Graves' Disease (GD) patients unwilling to undergo **RAI therapy**.
- **Preliminary control** before **RAI or surgery**.
- **Safe option for pregnancy** and **neonatal Graves' disease**.
- To assess if **mild hyperthyroidism symptoms** are genuine before permanent treatments.

### Types of Anti-Thyroid Drugs

| Drug Type | Examples | Mechanism of Action |
|---|---|---|
| **Thiourea Drugs** | **PTU (Propylthiouracil), MMI (Methimazole)** | Inhibit **thyroid peroxidase**, reducing hormone production. |
| **PTU-Specific Action** | PTU | Also decreases **T4 to T3 conversion** in peripheral tissues. |
| **Potency** | MMI | **10 times more potent** than PTU. |

### Effectiveness & Duration

- **Remission rate:** 40-50%.
- More effective in:
  - **Older patients**.
  - **Low T4/T3 ratio**.
  - **Short disease duration (<6 months)**.
  - **No previous relapse history**.
- **Therapy duration: 1 to 2 years** or longer.
- **Follow-up:** Every **6 to 12 months** after remission.
- **Time to become euthyroid: 3-8 weeks**.

---

## 2. **Radioactive Iodine (RAI) Therapy**

- **Preferred treatment for Graves' Disease (GD) and Toxic Nodular Goiter (TNG).**
- **Beta blockers** may be given to control symptoms.
- **Outcomes:**
  - **60% of patients euthyroid** within **6 months**.
  - **40% require multiple doses**, becoming euthyroid within **1 year**.
- **Repeat RAI dose:** After **6 months** if needed.
- **Precautions:**
  - **In the UK, nursery school teachers are advised to stay home for 3 weeks** after a 15-mCi **I-131 dose** due to radiation exposure.
- **Time to become euthyroid: 1-2 months**.

---

### 3. **Surgical Management (Thyroidectomy)**

#### When is Surgery Recommended?

- **Large thyroid gland** (>80 g).
- **Severe ophthalmopathy** (eye complications in Graves' disease).
- **Failure to achieve remission** with anti-thyroid drugs.

Surgery is usually a last resort when **medications and RAI are ineffective** or **contraindicated**.

---

## Thyroid Storm:

| Drug | Regimen |
|---|---|
| Propylthiouracil | 900–1200 mg/day orally in four or six divided doses |
| Methimazole | 90–120 mg/day orally in four or six divided doses |
| Propranolol | 40–80 mg every 6 h |
| Dexamethasone | 5–20 mg/day orally or IV in divided doses |
| Prednisone | 25–100 mg/day orally in divided doses |
| Methylprednisolone | 20–80 mg/day IV in divided doses |
| Hydrocortisone | 100–400 mg/day IV in divided doses |

# Thyroiditis: Treatment Approach

**Management of Mild Symptomatic Thyroiditis:** Patients with **mild symptoms** are initially treated with:

1. **β-Adrenergic Blockers (Beta-Blockers)** – To control **heart rate, tremors, and anxiety**.
2. **NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)** – To **reduce inflammation and pain**.

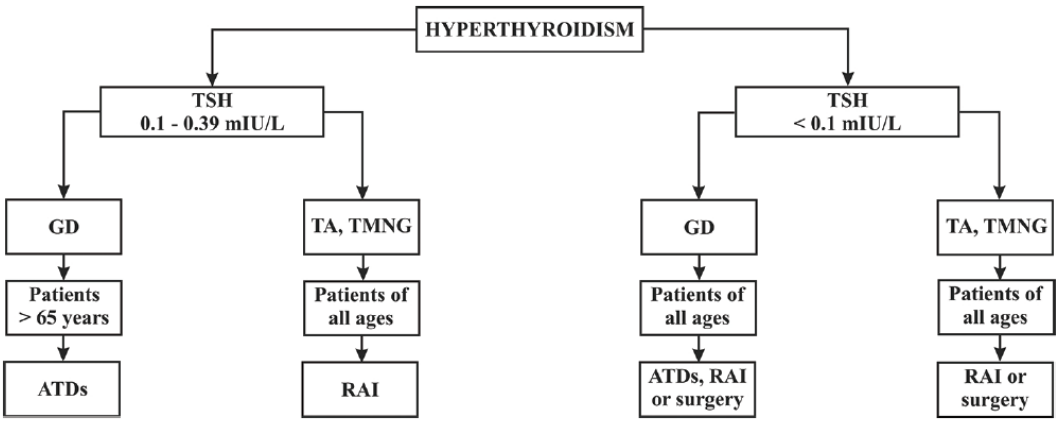
### Additional Treatment Options (For Severe Cases)

- **Corticosteroids** – Used if **inflammation is severe or autoimmune-related**.
- **Levothyroxine** – Given if the patient develops **hypothyroidism** after thyroid inflammation.

---

## Simplified Hyperthyroidism Management Flowchart

1. **Check TSH Levels:**
   - **TSH 0.1 - 0.39 mIU/L**
     - **Graves' Disease (GD):**
       - If age **>65 years** → Treat with **ATDs (antithyroid drugs).**
     - **Toxic Adenoma (TA) / Toxic Multinodular Goiter (TMNG):**
       - **All ages** → Treat with **RAI (radioactive iodine).**
   - **TSH < 0.1 mIU/L**
     - **Graves' Disease (GD):**
       - **All ages** → Treat with **ATDs, RAI, or surgery.**
     - **Toxic Adenoma (TA) / Toxic Multinodular Goiter (TMNG):**
       - **All ages** → Treat with **RAI or surgery.**



# Hypothyroidism

## Definition

Hypothyroidism is a condition where the thyroid gland does not produce enough thyroid hormones. It leads to various clinical symptoms and biochemical changes in the body.

## Types of Hypothyroidism

| Type | Description |
|---|---|
| **Underactive Thyroid** | A general term for a thyroid that is not producing enough hormones. |
| **Subclinical Hypothyroidism** | A mild form where hormone levels are slightly low, but symptoms may not be obvious. |
| **Overt Hypothyroidism** | A more severe form with noticeable symptoms and clear hormone deficiencies. |
| **Primary Hypothyroidism** | Caused by a problem in the thyroid gland itself, leading to reduced hormone production. |
| **Secondary Hypothyroidism** | Caused by issues in the pituitary gland or hypothalamus, which control the thyroid gland. |

---

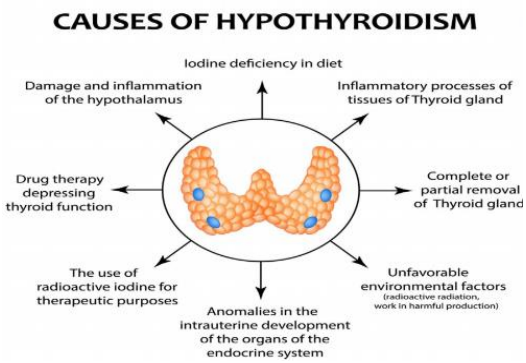
**TSH Range:**

| TSH Level (mU/L) | Condition |
|---|---|
| 0.0 – 0.4 | Hyperthyroidism or suppressed TSH |
| 0.4 – 4.0 | Normal range of TSH |
| 4.0 – 10.0 | Subclinical (mild) hypothyroidism |
| 10.0 + | Hypothyroidism |

---

## Causes of Hypothyroidism:

- Iodine deficiency in the diet
- Inflammatory processes affecting thyroid tissues
- Complete or partial removal of the thyroid gland
- Unfavorable environmental factors (radioactive radiation, harmful work conditions)
- Congenital anomalies in intrauterine development
- Use of radioactive iodine for therapeutic purposes
- Drug therapies that suppress thyroid function
- Damage and inflammation of the hypothalamus



# Classification of Hypothyroidism:

Hypothyroidism is classified into three types based on the underlying cause:

## 1. Primary Hypothyroidism

- **Cause:** Dysfunction or damage to the thyroid gland itself.
- **Common Causes:**
  - Iodine deficiency
  - Hashimoto's thyroiditis (autoimmune disease)
  - Congenital thyroid disorders
  - Post-surgical or post-radioactive iodine treatment
  - Certain medications (e.g., lithium, amiodarone)
- **TSH Levels:** High
- **T3/T4 Levels:** Low

## 2. Secondary Hypothyroidism

- **Cause:** Dysfunction of the pituitary gland, leading to insufficient Thyroid-Stimulating Hormone (TSH) production.
- **Common Causes:**
  - Pituitary tumors
  - Pituitary surgery or radiation damage
  - Traumatic brain injury
  - Sheehan's syndrome (postpartum pituitary failure)
- **TSH Levels:** Low or normal
- **T3/T4 Levels:** Low

## 3. Tertiary Hypothyroidism

- **Cause:** Dysfunction of the hypothalamus, leading to decreased Thyrotropin-Releasing Hormone (TRH) production, which in turn affects the pituitary and thyroid.
- **Common Causes:**
  - Hypothalamic tumors
  - Brain injuries or surgeries affecting the hypothalamus
  - Chronic illnesses affecting hypothalamic function
- **TSH Levels:** Low
- **T3/T4 Levels:** Low

---

## Etiology (Causes) of Hypothyroidism

### 1. Congenital Hypothyroidism (Present from birth)

- **Caused by mutations affecting:**
  - Thyroid gland development
  - Iodine absorption
  - Enzymes required for thyroid hormone (T4) production

- Thyroid-Stimulating Hormone (TSH) receptor

**2. Hashimoto's Thyroiditis (Autoimmune Cause)**

- **An autoimmune condition leading to:**
  - Enlargement of the thyroid (goiter) or thyroid atrophy
  - Antibody-mediated damage to the thyroid gland
- **Antibodies target:**
  - Thyroid peroxidase (TPO)
  - Thyroglobulin
  - Other thyroid cell membrane components

**3. Iatrogenic Hypothyroidism (Caused by Medical Treatment)**

- **Possible causes:**
  - Thyroid surgery
  - Radioactive iodine (RAI) treatment for Graves' disease
  - Use of lithium carbonate (a medication for mood disorders)
  - Excessive iodine intake from medications (e.g., expectorants)

**4. Secondary Hypothyroidism (Caused by Pituitary Gland Issues)**

- **Due to inadequate TSH production by the pituitary gland**
- **Possible causes:**
  - Pituitary tumors
  - Pituitary surgery
  - Radiation therapy targeting the pituitary gland
  - Postpartum pituitary necrosis (Sheehan's syndrome)
  - Metastatic cancers affecting the pituitary

**5. Hypothalamic Hypothyroidism (Rare Cause)**

- **Due to problems in the hypothalamus, leading to insufficient TRH (Thyrotropin-Releasing Hormone) production**
- **Possible causes:**
  - Cranial radiation therapy
  - Head trauma
  - Tumors affecting the hypothalamus

---

## Signs & Symptoms:

- Dry hair
- Loss of eyebrow hair
- Puffy face
- Enlarged thyroid (goiter)
- Slow heartbeat
- Arthritis
- ❄ Cold intolerance
- Depression
- Dry skin
- Fatigue
- Forgetfulness
- Menstrual disorders
- Infertility
- Muscle aches
- Weight gain
- Constipation
- Brittle nails

## Diagnosis and Treatment of Hypothyroidism

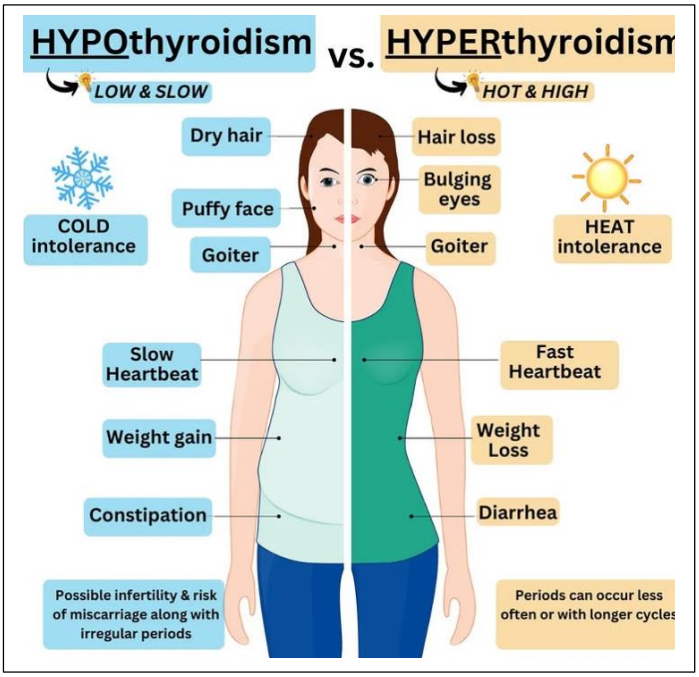
## Diagnosis:

| Method | Description |
|---|---|
| **Physical Exam** | The doctor checks for symptoms like fatigue, weight gain, dry skin, slow heart rate, and swelling in the neck (goiter). |
| **Thyroid Function Tests (TFTs)** | Blood tests to measure hormone levels: - **TSH (Thyroid-Stimulating Hormone)** – High in primary hypothyroidism, low in secondary hypothyroidism. - **T3 & T4 (Thyroid Hormones)** – Low in hypothyroidism. |
| **Thyroid Scan** | Imaging test to check the size, shape, and function of the thyroid gland. |
| **Thyroid Biopsy** | A small sample of thyroid tissue is taken to check for diseases like cancer or inflammation. |

---

## Treatment

| Treatment | Description |
|---|---|
| **Thyroxine (T4 Hormone Replacement)** | A synthetic hormone (Levothyroxine) that replaces the missing thyroid hormones and helps restore normal body functions. It is taken as a daily pill. |



# Hypopituitarism

## Introduction

- **Pan hypopituitarism** is a condition where the pituitary gland fails to produce **multiple** hormones.
- **First described in 1914 by Simmonds**, also known as **Simmonds' disease**.
- **Types:**
  - **Hypopituitarism** – Deficiency in **one or more** pituitary hormones.
  - **Panhypopituitarism** – **Complete** loss of pituitary function (deficiency of **all** hormones).
- **Prevalence:** 4–21 cases per 100,000 people.

---

## Causes (Etiology) of Hypopituitarism

| Category | Examples |
|---|---|
| **1. Pituitary & Hypothalamic Mass Lesions** | Tumors pressing on the pituitary gland. |
| **2. Pituitary Surgery** | Surgery-related damage to the pituitary. |
| **3. Radiotherapy** | Radiation treatment affecting pituitary function. |
| **4. Trauma & Vascular Injury** | Brain injuries or stroke affecting blood flow to the pituitary. |
| **5. Infiltrative Disorders** | Conditions like sarcoidosis that invade pituitary tissue. |
| **6. Infections** | Tuberculosis, meningitis, or other infections. |
| **7. Immune System Disorders** | Autoimmune diseases attacking the pituitary. |
| **8. Genetic Causes** | Inherited disorders affecting pituitary development. |

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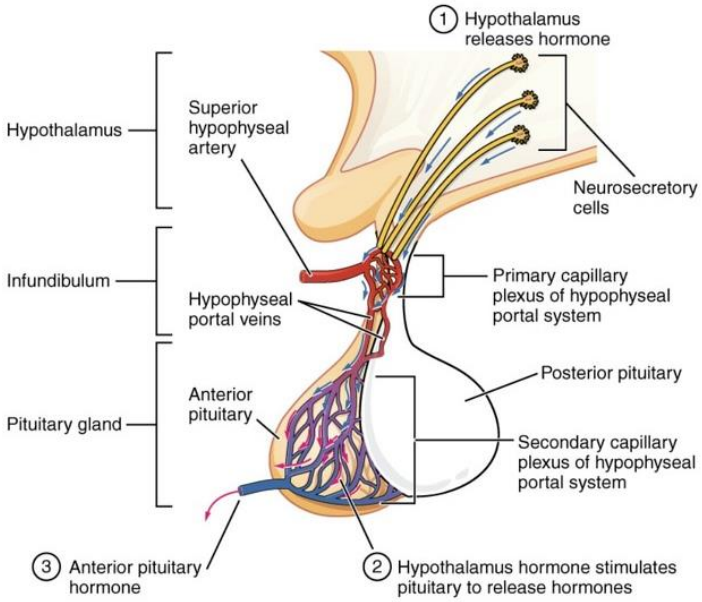
### Pituitary Gland – Master Gland:



## Etiology:

| Category | Causes |
|---|---|
| **Neoplastic (Tumors)** | Pituitary adenoma, Craniopharyngioma, Meningioma, Cysts (Rathke's cleft, arachnoid, epidermoid, dermoid), Germinoma, Glioma, Astrocytoma, Ganglioneuroma, Paraganglioma, Teratoma, Chordoma, Pituicytoma, Ependymoma, Pituitary carcinoma, Metastases |
| **Infectious** | Bacterial, Fungal, Parasitic infections, Tuberculosis, Syphilis |
| **Vascular** | Pituitary tumor apoplexy, Sheehan's syndrome, Intracranial carotid artery aneurysm, Subarachnoid hemorrhage |
| **Traumatic** | Head injury |
| **Medications** | Opiates (affect ACTH, GH), Glucocorticoids (ACTH), Megestrol acetate (ACTH), Somatostatin analogs (GH, ACTH, TSH), CTLA-4 blockers (ACTH, TSH, LH/FSH) |
| **Infiltrative/Inflammatory** | Autoimmune (lymphocytic hypophysitis), Hemochromatosis, Granulomatous (granulomatosis with polyangiitis, sarcoidosis), Langerhans cell histiocytosis, Giant cell granuloma, Xanthomatous hypophysitis |
| **Structural/Idiopathic** | Empty sella syndrome, Idiopathic (unknown cause) |
| **Treatment** | Surgery, Radiotherapy |

---

## Clinical Presentation:

| Category | Symptoms |
|---|---|
| **Acute** | • Headache, nausea, vomiting,<br>• hypotension (low blood pressure), hyponatremia (low sodium levels),<br>• high mortality rate |
| **Chronic** | • Increased fat, low muscle mass (GHD), infertility, loss of body hair,<br>• menstrual irregularities, loss of libido, TSH deficiency,<br>• lethargy, tiredness, weight loss, ADH & prolactin deficiency |

---

## Diagnosis and Management of Hypopituitarism

| Category | Details |
|---|---|
| **Physical Examination** | Examination of the thyroid, genital organs, body hair, and scalp hair. Checking BMI (Body Mass Index). |
| **Laboratory Tests** | Measuring cortisol and ACTH (adrenal hormones), TSH and T4 (thyroid hormones), IGF-I (growth hormone-related), and arginine vasopressin test (fluid balance). |
| **Imaging** | MRI scans and CT brain scans to detect pituitary abnormalities. |

### Non-Pharmacological Management

- **Good gynecological care** to prevent hormonal issues.
- **Radiation prevention** to avoid pituitary damage.
- **Careful pituitary surgeries** to minimize complications.
- **Experienced neurosurgeons** using high-resolution microscopes can reduce the risk of hypopituitarism (hormone deficiencies).

---

## Goals of Pharmacotherapy

- Restore hormone levels to normal.
- Lifelong hormone replacement therapy is often required.
- Patients may need **higher glucocorticoid doses** during stress (illness, emotional strain) to prevent serious complications.

---

## Treatment Options

| Type | Examples |
|---|---|
| **Hormone Replacement** | Glucocorticoids, Estrogens, Progesterone, Testosterone, Growth Hormone (GH) replacement |
| **Surgical Management** | Surgery to remove pituitary adenomas (tumors) |

# Acute Kidney Injury (ARF)

**Chapter 10 - Unit IX Nephrology**

## Contents



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## Acute Renal Failure (ARF)

- ARF or AKI (Acute Kidney Injury) is a **sudden and rapid decline** in renal filtration function.
- **Symptoms:**
  - Decreased urine output.
  - Increase in Serum Creatinine (Scr) or Blood Urea Nitrogen (BUN).
- **Reversibility:** If managed early, it is reversible.
- **Severity:**
  - Delayed diagnosis leads to high mortality and morbidity.
  - Affects **5% of hospitalized patients**.
  - High prevalence in **ICUs and multi-organ failure patients**.
  - **AKI mortality rate is 46.5%**.
  - **200 cases per million people in the USA**.

---

## ARF Classification

### 1. Prerenal (55%)

- **Causes:**
  - Severe volume depletion.
  - Hypotension.
- **Nephrons remain structurally intact**.

### 2. Intrinsic (40%)

- Caused by cytotoxic, ischemic, or inflammatory injury to the kidneys.
- Leads to **structural and functional kidney damage**.

### 3. Postrenal (5%)

- **Obstruction in urine passage** due to:
  - Stones
  - Tumors
  - Urethral obstruction (e.g., enlarged prostate)

---

# ARF Classification Based on Urine Output

1. **Anuria** (<50 ml/day)
   - **High mortality, less reversible**.
2. **Oliguria** (50-450 ml/day)
   - **High mortality, less reversible**.
3. **Non-Oliguria** (>450 ml/day)
   - **Better prognosis, lower risk of fluid overload**.

---

# Etiology of ARF

### 1. Prerenal Causes

- **Volume Depletion:** Diuretics, GI losses, burns, hemorrhage.
- **Cardiac Issues:** Heart failure, hypotension.
- **Other:** Liver failure, sepsis.

### 2. Intrinsic Causes

- **Vascular:** Renal artery/vein obstruction, transplant rejection, malignant hypertension.
- **Glomerular:** Glomerulonephritis, autoimmune diseases.
- **Tubular:** Aminoglycoside toxicity, rhabdomyolysis.
- **Interstitial:** Inflammatory kidney diseases.

### 3. Postrenal Causes

- **Tubular Obstruction:** Crystals (e.g., uric acid, calcium oxalate).
- **Ureteral Obstruction:** Stones, tumors, fibrosis.
- **Urethral Obstruction:** Benign prostatic hypertrophy (BPH), neurogenic bladder, stones.

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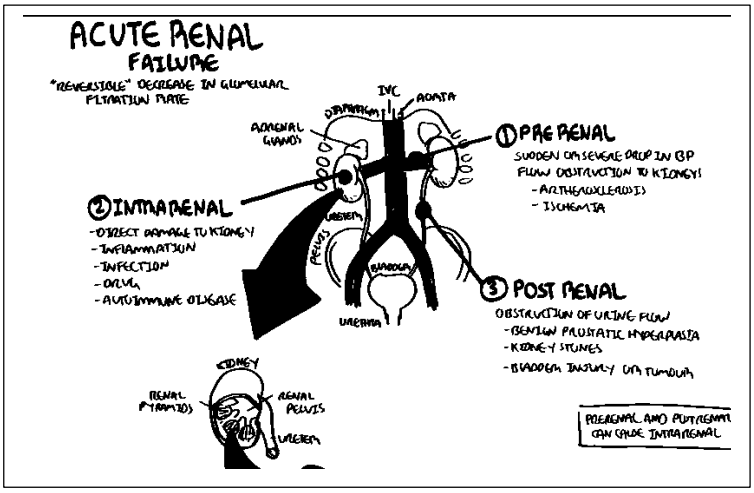



**Table 1. Etiological Subgroups of ARF in Hospitalized Patients.**

| S.No. | Etiological Group | Etiological Sub Group | Number of Cases | Total |
|---|---|---|---|---|
| 1 | Medical | Gastroenteritis | 24 | 75 |
| | | Sepsis | 16 | |
| | | Myocardial infarction and CHF | 10 | |
| | | Malaria | 9 | |
| | | Cerebro vascular accident | 6 | |
| | | Pancreatitis | 5 | |
| | | Chronic liver disease | 2 | |
| | | Rhabdomyolysis | 2 | |
| | | Autoimmune hemolytic anemia | 1 | |
| 2 | Surgical | Laprotomy | 5 | 17 |
| | | Cholecystectomy | 4 | |
| | | CABG | 3 | |
| | | Miscellaneous | 3 | |
| | | Orthopedics Surgeries | 2 | |
| 3 | Obstetrics | Postpartum hemorrhage | 3 | 5 |
| | | Eclampsia | 2 | |
| 4 | Others | | 3 | 3 |
| | Grand Total | | | 100 |

JPMA 55:526;2005

# Stages of ARF

| Stage | Serum Creatinine (SCr) | Urine Output |
|---|---|---|
| **Stage 1** | 1.5–1.9x baseline or >0.3 mg/dL increase | <0.5 mL/kg/h for 6–12h |
| **Stage 2** | 2.0–2.9x baseline | <0.5 mL/kg/h for >12h |
| **Stage 3** | 3.0x baseline or SCr >4.0 mg/dL | <0.3 mL/kg/h for >24h or Anuria for >12h |

---

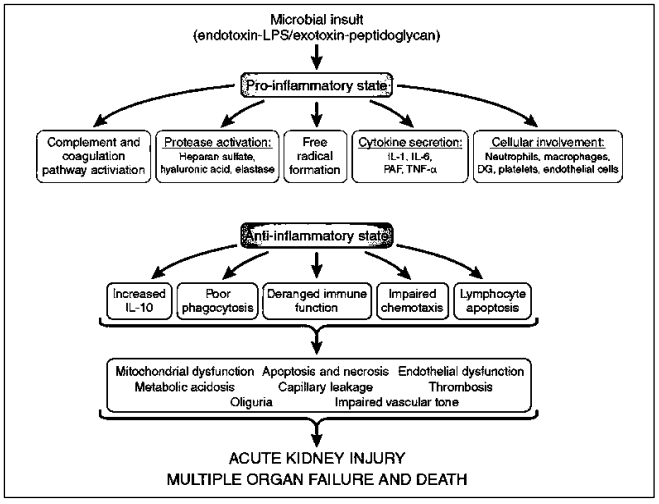
# Pathophysiology of ARF

## Key Mechanisms

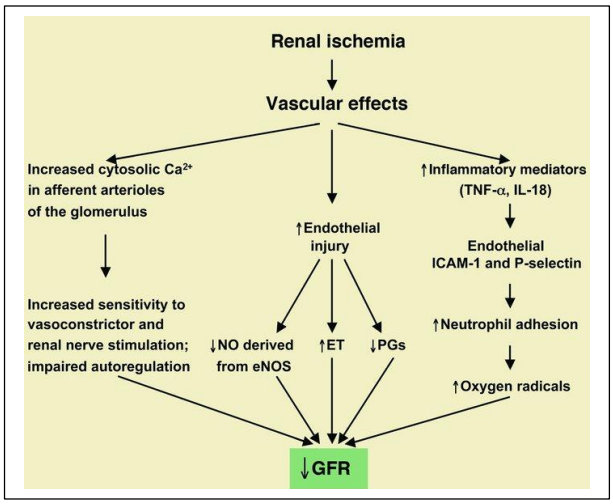
1. **Inflammation:** Cytokine and Leukocyte Activation
2. **Toxic Injury** : Direct Tubular Injury, Antibiotics Contrast.
3. **Ischemia**: Microcirculatory Failure and Hypoxia
4. **Reactive Oxygen Species (ROS) and Mitochondrial Dysfunction**
5. **Endothelial Dysfunction**
6. **Coagulation Dysfunction**

---

**ARF Pathophysiology in Septic Conditions:**




**ARF Pathophysiology Vasculature:**



## Signs & Symptoms: Vary from patient to patient Stage and etiological factors

- **Prerenal Symptoms:**
  - Dehydration (thirst, dizziness, orthostatic hypotension).
  - **Altered mental status**.
- **Intrinsic Symptoms:**
  - Fever, rash, muscle pain, **seizures**.
- **Postrenal Symptoms:**
  - BPH (Benign Prostatic Hyperplasia), **urinary urgency, frequency, hesitancy**.
  - Flank pain, **hematuria**.
- **General Symptoms:**
  - **Hypertension, edema**.

---

# Diagnosis of ARF

1. **Medical History & Physical Examination**
2. **Laboratory Tests:**
   - Complete Blood Count (CBC) & Biochemistry
   - Urinalysis & Electrolytes
3. **Radiological Exams/Imaging:**
   - Ultrasound, CT scan, MRI

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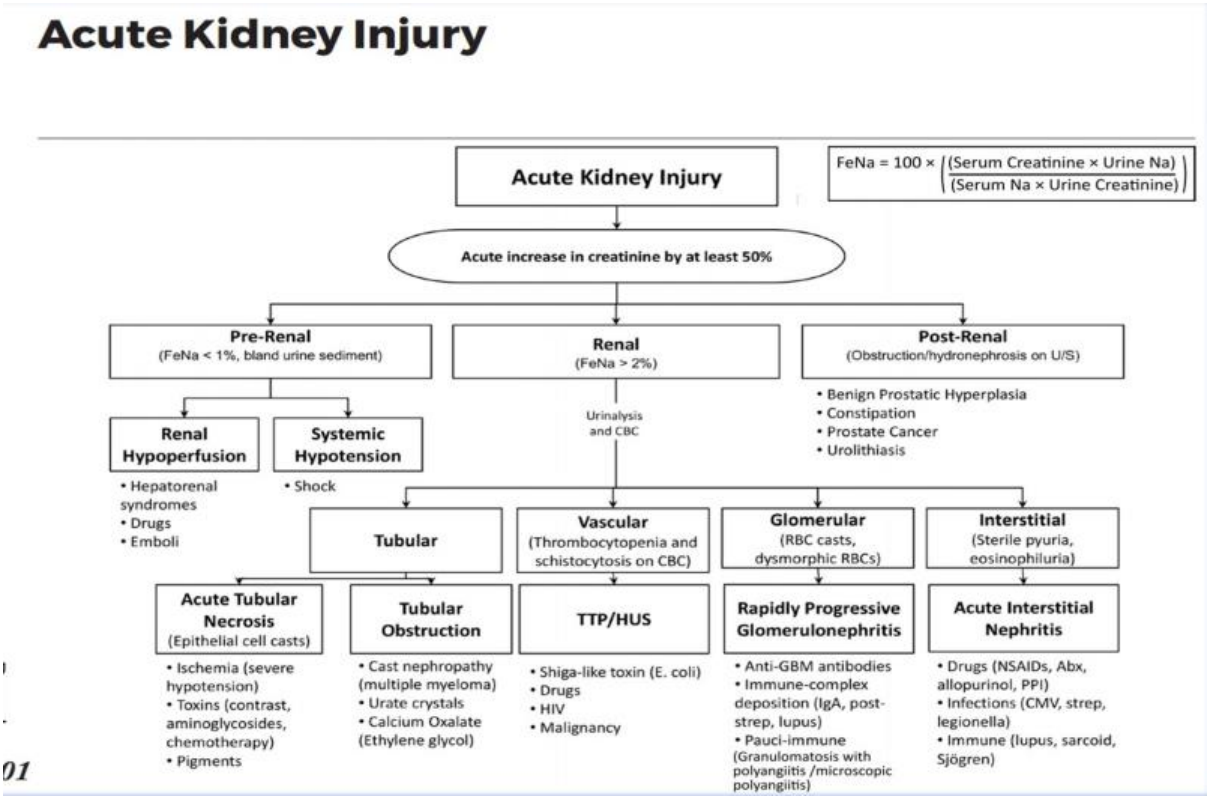

# Management of ARF

## Goals of Treatment

- **Prevent ARF and its progression**.
- **Key interventions:**
  - Theophylline, acetylcysteine, insulin, hydration (sodium loading), glycemic control.

## Supportive Management

1. **Fluid Management**
   - Blood pressure and cardiac output monitoring.
   - Maintain **tissue perfusion**.
2. **Electrolyte Management**
   - Correct **sodium, potassium, calcium imbalances**.
3. **Management of Edema**
   - **Diuretics if needed**.
4. **Renal Replacement Therapy (RRT)**
   - Continuous or intermittent **dialysis** for severe cases.
5. **Acid-Base Balance and Intoxication Management**.

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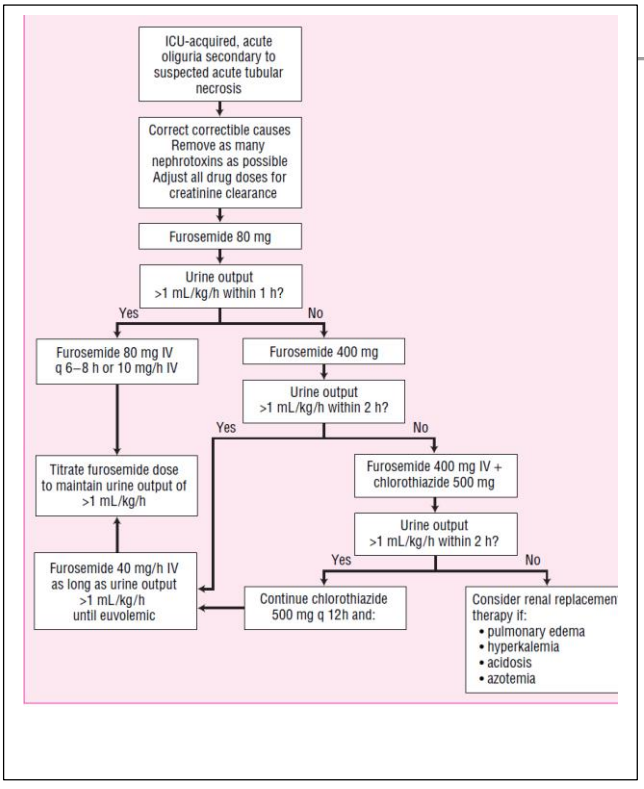
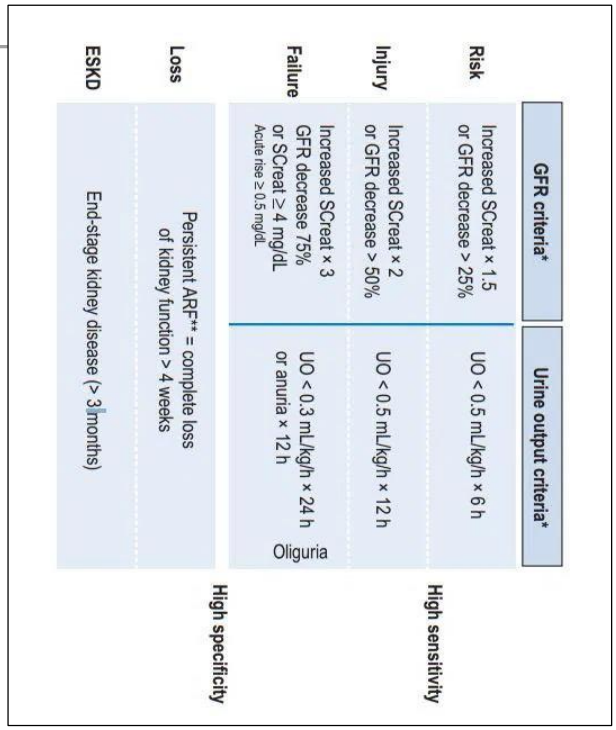
# ARF ATN ICU Algorithim




# RIFLE Criteria for AKI



# Urinary Tract Infection (UTI)

## Case Study: Ms. Shaheen

- **Age:** 73 years
- **Occupation:** Housewife
- **Condition:** Anxious/distressed for the past 3 days
- **Symptoms:**
  - Dysuria (painful urination) and urinary frequency
  - Urgency leading to incontinence
  - Episode of hematuria (blood in urine)
  - Lower abdominal discomfort
  - Cloudy or foul-smelling urine
- **Diagnosis:** Urine culture revealed **E. coli**
- **Prescription:**
  - **Trimethoprim/Sulfamethoxazole**
  - **Cranberry Juice**

---

## Introduction to UTI

- **Definition:** Presence of microorganisms in the urinary tract, invading tissues and adjacent structures.
- **Types:**
  - **Asymptomatic**
  - **Symptomatic** (can lead to bacteremia or sepsis)
- **Prevalence:**
  - Common in boys during infancy
  - More common in females aged 1-5 years

---

## Classification of UTI

### Based on Anatomy

- **Upper UTI:** Affects kidneys and ureters
- **Lower UTI:** Affects bladder and urethra

### Based on Clinical Presentation

- **Uncomplicated UTI:** Occurs in healthy individuals with normal urinary tracts
- **Complicated UTI:** Associated with structural abnormalities, catheter use, or underlying diseases
- **Recurrent UTI:** Multiple episodes over time

# Pathophysiology

- **Route of Infection:**
  - **Ascending (95%)** – Fecal flora, contraceptive materials
  - **Descending (5%)** – Bloodborne (hematogenous route)
- **Common Pathogen: E. coli (85%)**
- **Host Defenses:**
  - Low pH, high urea concentration, prostatic secretions, diuresis, mucosal protection
- **Risk Factors:**
  - Obstruction, neuropathies, kidney stones, BPH (benign prostatic hyperplasia), vesicourethral reflux, diabetes, pregnancy, stroke, catheterization

---

# Signs and Symptoms

| Type | Symptoms |
|---|---|
| **Lower UTI (LUTI)** | Dysuria, urgency, frequency, nocturia, suprapubic heaviness, gross hematuria |
| **Upper UTI (UUTI)** | Flank pain, fever, nausea, vomiting, malaise |

---

# Diagnosis

## Physical Examination

- Costovertebral tenderness

## Laboratory Tests

- **Urine Collection Methods:**
  - Midstream clean catch
  - Catheterization
  - Suprapubic bladder aspiration
- **Findings:**
  - Bacteria, proteinuria, hematuria, pyuria
  - Urine routine examination (Urine R/E)
  - Urine culture

## Imaging

- **Ultrasound (U/S)**
- **X-ray**

---

# Management of UTI

### Goals of Treatment

- Prevent or treat systemic consequences of infection
- Eradicate the invading organism
- Prevent recurrence

### Pharmacologic Therapy

- **NSAIDs (for pain relief)**
- **Cranberry sachets** (for prevention)
- **Antibiotics** (as per type of UTI)

---

## Antibiotic Therapy for Uncomplicated UTI

| Type of UTI | Antibiotic | Dose | Duration |
|---|---|---|---|
| **Uncomplicated** | Sulfamethoxazole/Trimethoprim | 1 DS BID | 3 days |
| | Ciprofloxacin | 250 mg BID | 3 days |
| **Pyelonephritis** | Ciprofloxacin | 250-500 mg BID | 14 days |

## Antibiotic Therapy for Complicated UTI

| Type of UTI | Antibiotic | Dose | Duration |
|---|---|---|---|
| **Complicated** | Sulfamethoxazole/Trimethoprim | 1 DS BID | 10 days |
| | Ciprofloxacin | 250-500 mg BID | 10 days |
| **Recurrent UTI** | Nitrofurantoin | 50 mg OD | 6 months |

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# Standard Treatment Guidelines (STGs)

- **NICE Guidelines** (National Institute for Health and Care Excellence) for UTI treatment and management

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# Thrombocytopenia

## Contents



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# Platelet Basics

- **Produced by**: Megakaryocytes
- **Normal Count**: 150,000 – 400,000/µL
- **First Described By**: James Homer (1906)
- **Lifespan**: 7-10 days
- **Distribution**:
  - 2/3 in circulation
  - 1/3 stored in the spleen
- **Function**:
  - Constantly monitor blood vessel endothelium
  - Play a key role in blood clotting (coagulation)
- **Clearance**: Removed from blood by macrophages in the spleen and liver

---

# Thrombocytopenia: Definition & Classification

- **Thrombocytopenia** – A condition where platelet count is **< 150,000/µL**
- **Severity Levels**:

| Severity | Platelet Count (per µL) | Clinical Features |
|---|---|---|
| **Mild** | 70,000 – 150,000 | Often asymptomatic |
| **Moderate** | 20,000 – 70,000 | May have minor bleeding |
| **Severe** | < 20,000 | High risk of spontaneous bleeding |

- **Bleeding Risks Based on Platelet Count:**

| Platelet Count (per µL) | Bleeding Risk |
|---|---|
| **> 50,000** | Usually no symptoms |
| **30,000 – 50,000** | Rarely presents with purpura (bruising) |
| **10,000 – 30,000** | Bleeding with minimal trauma |
| **< 10,000** | Spontaneous bleeding (petechiae, bruising) |
| **< 5,000** | High risk of mucosal, intracranial, gastrointestinal, and genitourinary bleeding |

# Etiological Classification of Thrombocytopenia

| Category | Causes |
|---|---|
| **1. Decreased Platelet Production** | Bone marrow failure, Bernard-Soulier syndrome, viral infections, liver cirrhosis, nutritional deficiencies, drug-induced |
| **2. Increased Platelet Destruction** | Immune thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulation (DIC), drug-induced thrombocytopenia (DIT), heparin-induced thrombocytopenia (HIT), HELLP syndrome, viral infections |
| **3. Sequestration (Platelet Pooling in Spleen)** | Hypersplenism, pseudothrombocytopenia |

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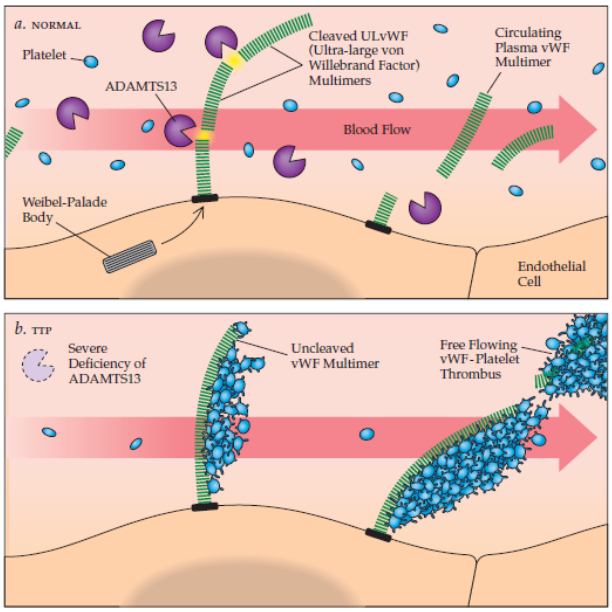
### Thrombotic Thrombocytopenic Purpura (TTP)




- A rare disorder in which small blood clots form throughout the body, blocking blood flow to vital organs.

1. **Normal Condition (Top Image)**
   - The body produces **von Willebrand Factor (vWF)** to help blood clot.
   - **ADAMTS13 enzyme** cuts large vWF molecules into smaller pieces.
   - This prevents excessive clotting, allowing normal blood flow.
2. **TTP Condition (Bottom Image)**
   - There is a **severe deficiency of ADAMTS13** (enzyme not working properly).
   - Large vWF molecules stay intact and trap platelets, forming clots inside blood vessels.
   - These clots block blood flow, leading to organ damage and a low platelet count.

**Key Issue in TTP:** Too many clots form inside blood vessels because vWF is not broken down properly.

## Thrombocytopenia DIC

### Disseminated Intravascular Coagulation (DIC)

- A life-threatening condition where blood clotting is massively activated throughout the body, leading to excessive clotting and bleeding at the same time.

### Simplified Explanation:

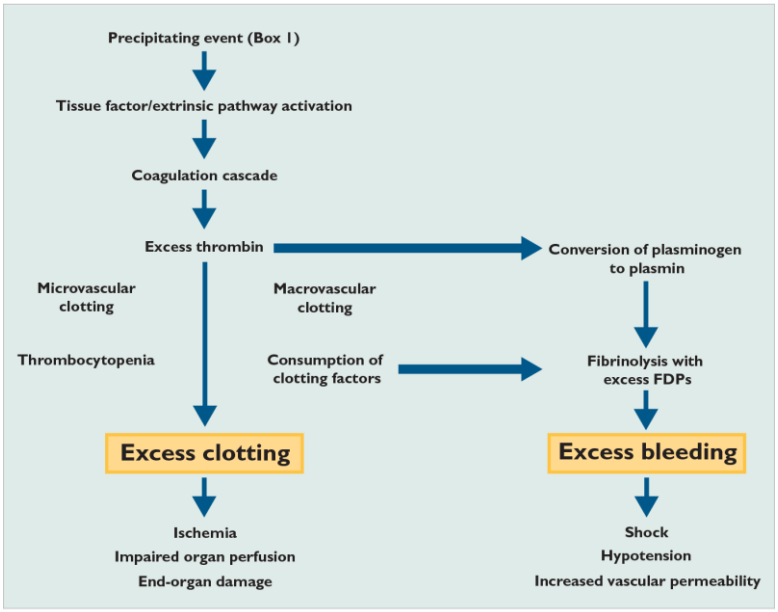


**Figure 1. Mechanisms leading to the development of DIC.** *FDP* = fibrin degradation products. (Adapted from Gobel BH. Disseminated intravascular coagulation in cancer: providing quality care. *Topics Adv Pract Nurs J* [online] 2002;2(4). Accessed October 2008

1. **Triggering Event:**
   - Something like infection, trauma, or cancer **activates blood clotting**.
2. **Clot Formation:**
   - The **coagulation process** goes into overdrive, producing **too much thrombin**, leading to **excessive clotting** in small and large blood vessels.
   - This causes **organ damage** (ischemia) and **low platelet count (thrombocytopenia)**.
3. **Clotting Factors Get Used Up:**
   - Since so many clots are being formed, the **body runs out of clotting factors**.
4. **Uncontrolled Bleeding Begins:**
   - The body tries to break down clots, but because clotting factors are depleted, **excessive bleeding** occurs.
   - This leads to **shock, low blood pressure, and increased risk of death**.

### Key Problem in DIC:

Body forms too many clots → Uses up clotting factors → Leads to uncontrolled bleeding.

While **TTP** involves abnormal clot formation due to an enzyme deficiency, **DIC** is a widespread clotting disorder triggered by an underlying illness, and **thrombocytopenia** simply refers to a low platelet count, which can occur in many conditions, including TTP and DIC.

## Thrombocytopenia Pathophysiology:

### Simplified Explanation:

1. **Platelet Production Starts from Stem Cells:**
   - Stem cells turn into **megakaryocytes**, which mature and release **platelets** into the blood.
2. **Problems in Platelet Production:**
   - **Hypoplasia:** Not enough stem cells producing megakaryocytes.
   - **Ineffective Thrombopoiesis:** Megakaryocytes fail to make platelets.
   - **Disordered Regulation:** Body is not properly controlling platelet production.
3. **Circulating Platelet Pool (Where Platelets Are Used):**

- Some platelets are stored in the spleen.
- Platelets are used up naturally or in response to injuries.

4. **Causes of Thrombocytopenia:**
   - **Abnormal pooling:** Too many platelets trapped in the spleen.
   - **Accelerated destruction:** Platelets are broken down too fast due to disease or immune response.

**Key Issue in Thrombocytopenia:**

Not enough platelets are made, or they are destroyed too quickly, leading to **increased bleeding risk**.

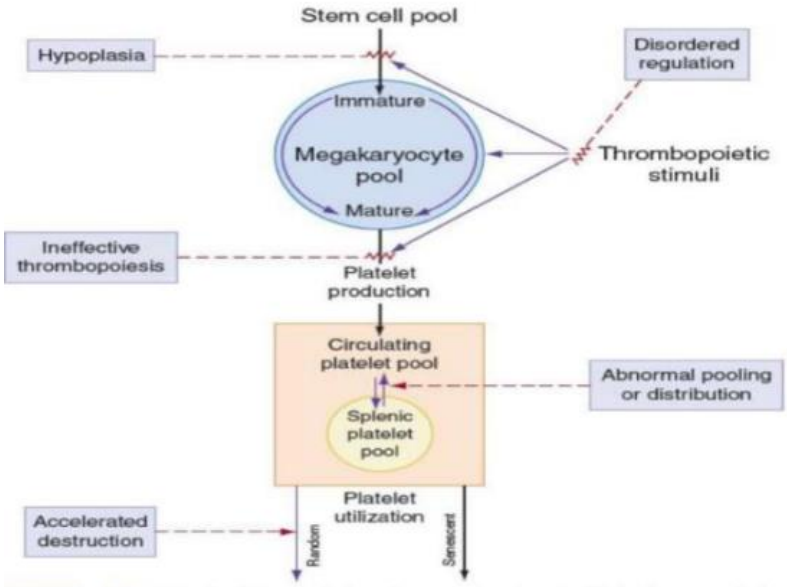



FIGURE 47.1 Pathophysiology of thrombocytopenia. A simplified diagram of the biodynamics of the megakaryocyte–platelet system (solid lines) and the mechanisms (dashed lines) by which pathologic processes (shaded blocks) produce thrombocytopenia.

# Signs and Symptoms of Thrombocytopenia

| Symptom | Description |
|---|---|
| **Ecchymosis** | Bruising without trauma |
| **Petechiae** | Small red or purple spots on the skin |
| **Itch-less Rash** | Non-itchy red or purple skin rash |
| **Epistaxis** | Nosebleeds |
| **Hemoptysis** | Coughing up blood |
| **Melena** | Black, tarry stools (due to internal bleeding) |
| **Prolonged Menstrual Periods** | Heavy or extended menstrual bleeding |
| **Hematuria** | Blood in urine |
| **Gum Bleeding** | Unexplained bleeding from the gums |

# Diagnosis of Thrombocytopenia

## 1. Patient History

- **Recent Infections** – Viral or bacterial illnesses
- **Malignancies** – Blood cancers affecting platelet levels
- **Pregnancy Status** – Important in premenopausal women
- **Recent Medications** – Drug-induced thrombocytopenia
- **Vaccinations** – Certain vaccines may trigger immune response
- **Recent Travels** – Exposure to infections or environmental factors
- **Recent Transfusions/Transplants** – Risk of immune reactions
- **Family History** – Genetic thrombocytopenia disorders
- **Autoimmune Disorders** – Conditions like lupus or rheumatoid arthritis

## 2. Physical Examination

| Findings | Clinical Indications |
|---|---|
| **Petechiae & Ecchymoses** | Small skin hemorrhages |
| **Mucocutaneous Bleeding** | Nosebleeds, gum bleeding |
| **Purpura** | Large purple skin patches |
| **Retinal Hemorrhages** | Bleeding in the eye |
| **Splenomegaly** | Enlarged spleen (common in sequestration thrombocytopenia) |
| **CNS Bleeding (Rare)** | Severe cases may present with brain hemorrhage |

---

# Laboratory Tests for Thrombocytopenia

| Test | Purpose |
|---|---|
| **Complete Blood Count (CBC)** | Measures platelet count and overall blood health |
| **Peripheral Blood Smear** | Examines platelet size, shape, and abnormalities |
| **D-dimer** | Checks for blood clotting issues |
| **Serum LDH (Lactate Dehydrogenase)** | Indicates cell breakdown, seen in TTP |
| **Bone Marrow Examination** | Evaluates platelet production in bone marrow |
| **HIV Test** | Rules out viral causes of thrombocytopenia |
| **ESR (Erythrocyte Sedimentation Rate)** | Detects inflammation and autoimmune disorders |
| **hsCRP (High-Sensitivity C-Reactive Protein)** | Assesses inflammation levels |

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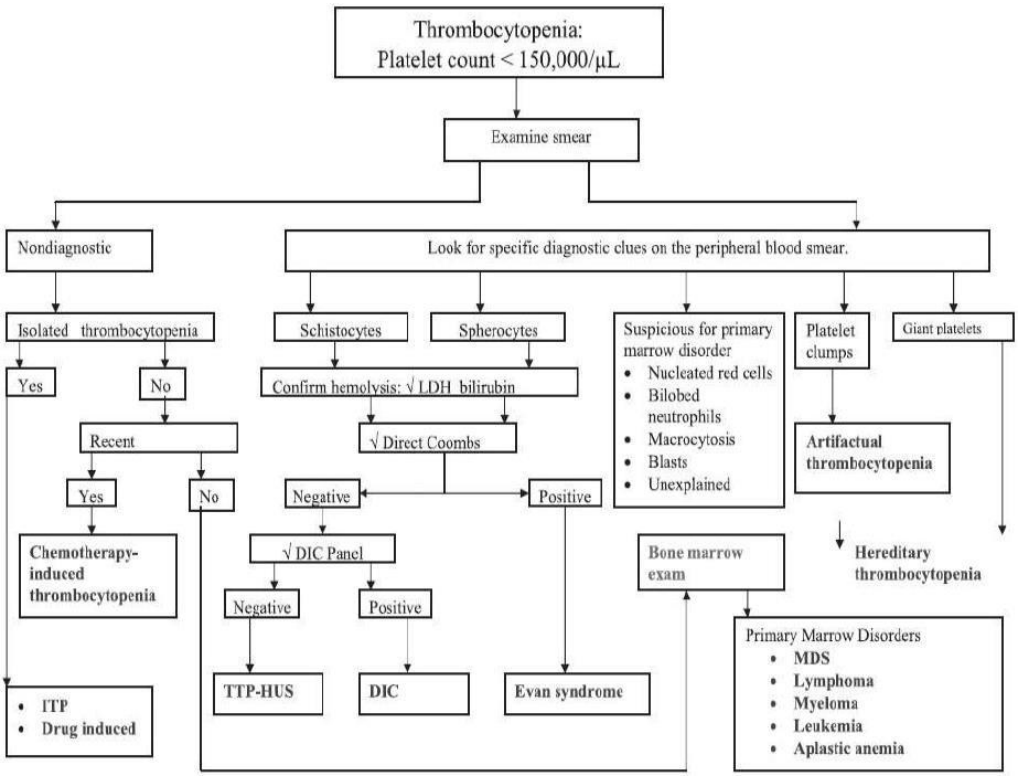

# Management of Thrombocytopenia

## Goals of Treatment

✓ Careful monitoring
✓ Prevent complications
✓ Minimize side effects
✓ Cost-effective therapy

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## General Management

| Cause | Management Approach |
|---|---|
| **Decreased Platelet Production** | Identify and treat the underlying cause |
| **Drug-Induced** | Discontinue and replace the causative drug |
| **Vitamin Deficiency** | Supplement **Vitamin B12** and **Folic Acid** |
| **Thrombopoietin** | Used to stimulate platelet production |
| **Severe Cases** | **Platelet transfusion** if needed |

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## Immune Thrombocytopenic Purpura (ITP) Management

| Condition | Treatment |
|---|---|
| **Platelet count < 20,000 – 30,000/µL** | Treatment required to prevent bleeding |
| **First-line treatment** | **Corticosteroids (Prednisolone for 2-3 weeks)** |
| **Persistent low platelets (< 30,000/µL after 4-6 weeks)** | **Splenectomy** |
| **Severe cases / Refractory ITP** | **IV Immunoglobulin (IV Ig) Therapy** |
| **Treatment-resistant cases** | **Rituximab** |
| **Pregnancy-associated ITP** | **IV Ig therapy** |

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## Thrombotic Thrombocytopenic Purpura (TTP) & Hemolytic Uremic Syndrome (HUS) Management

| Condition | Treatment |
|---|---|
| **TTP & HUS** | Fresh frozen plasma transfusion |
| **Severe cases** | Rituximab |

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## **HELLP (**Hemolysis, Elevated Liver enzymes and Low Platelets) **Syndrome Management**

| Condition | Treatment |
|---|---|
| **HELLP Syndrome (Pregnancy-related)** | Immediate termination of pregnancy |
| **Mild cases** | Corticosteroids |

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## Platelet Sequestration Management

- **Treat the underlying condition** (e.g., hypersplenism, liver disease)

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